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ON GENDER DYSPHORIA

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On Gender Dysphoria

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To mom and dad for not hindering my *profite la vie* attitude, for encouraging me to discover the world, and for always welcoming anyone and everyone to Sunday dinner.

ABSTRACT

Gender identity refers to an innate and deeply felt psychological identification as a female, male, or some other non-binary gender. Gender identity may be congruent or incongruent with the sex assigned at birth. Gender dysphoria refers to the discomfort or distress that gender incongruence may cause. If the distress is clinically significant, the individual may need gender-affirming treatment. The literature is sparse with respect to the etiology, prevalence, and long-term outcomes. The overall aim of this thesis is to further our understanding of gender dysphoria regarding neurobiological characteristics, epidemiology, and health following gender-affirming treatment. **Study I** explored the hypothesis that cerebral activation in hormone-naïve transgender women (assigned males at birth) on exposure to odorous steroids would be in line with their gender identity, and thus similar to cisgender women but different to cisgender men. Gender dysphoric transgender women demonstrated a cerebral activation pattern that corresponded predominately to that of cisgender females, but also some cisgender male characteristics. **Study II** described the prevalence and changes in incidence of applications for change of legal gender and applications to reverse the procedure during 1960-2010. The incidence of gender dysphoria increased three times for individuals assigned male at birth, and two and half time times for individuals assigned female at birth. The increase accelerated after 2001. The rate of reversal applications was 2.2% with a significant decline over the study period. **Study III** explored long-term mortality and psychiatric morbidity after sex reassignment in a nation-wide cohort study (1973-2003). The overall mortality rate was higher in individuals who had undergone legal and medical transition compared with the general population for the whole period, but not for the period 1989-2003. Probands had more psychiatric inpatient care and suicide attempts compared with controls for the whole period as well as the period 1989-2003 (with the exception of suicide attempts). This study cannot determine the effectiveness of gender-affirming medical intervention, but the results highlight the need for better health care following gender transition. **Study IV** examined outcomes following legal and surgical gender transition, mean (SD) follow-up time 7.2 (7.3) years, by means of individual interviews with 16 men (assigned female at birth) and 49 women (assigned male at birth). The vast majority of the participants felt gender congruent and global clinically improved, but the prevalence of psychiatric morbidity and suicide attempts was high. Childhood adversities and adult stressful life events were common. Being born abroad, childhood adversities, and not being accepted by others in assigned gender predicted current psychiatric morbidity.

SAMMANFATTNING

En persons könsidentitet beskriver den inre upplevelsen av könstillhörighet. Den kan vara kvinnligt, manligt eller något ickebinärt kön. Könsinkongruens innebär att en persons könsidentitet inte stämmer överens med det kön som blev tilldelat vid födseln. Könsdysfori är det lidande som könsinkongruens ibland orsakar. I de fall lidandet är uttalat kan personer behöva könsbekräftande behandling. Bakgrunden till könsdysfori, hur vanligt det är och hur en person mår efter behandling är ofullständigt känt. Det övergripande syftet med denna avhandling var öka kunskapen om könsdysfori avseende neurobiologiska karakteristiska, epidemiologi och hälsa efter könsbekräftande behandling. **Studie I** undersökte om transkvinnor (personer som tillskrivits manligt kön vid födseln men identifierar sig som kvinnor) aktiverade hjärnan på liknande sätt som ciskvinnor eller cismän (cispersoner = personer utan könsinkongruens eller könsdysfori) när de exponeras för feromoner Transkvinnor uppvisade ett aktiveringsmönster mer likt ciskvinnor men med en del cismanliga drag. I **studie II** har vi beskrivit incidensen av ansökningar om ändring av juridiskt kön samt tillstånd för operation av könsorganen under 1960-2010. Vi undersökte även antalet ansökningar om återgång till det ursprungliga könet. Vi fann att incidensen ökade tre gånger för dem som tillskrivits manligt kön vid födseln och två och en halv gång för dem som tillskrivits kvinnligt kön. Ökningen var mest uttalad efter 2001. Av de som beviljats ändring av juridiskt kön ansökte 2,2 % om att få återgå till ursprungligt kön. Antalet ångeransökningar minskade signifikant under den senare delen av tidsperioden. I **studie III** undersöktes överlevnad och psykiatrisk sjuklighet i en nationell kohort av personer som bytt juridisk kön och genomgått kirurgisk könsbekräftande behandling mellan 1973-2003. För hela tidsperioden fann vi en förhöjd dödlighet och att vård för psykisk sjukdom och självmordsförsök var vanligare jämfört med befolkningskontroller. Under den studerade perioden sågs en minskning avseende dödlighet och vård för självmordsförsök, där de som bytt juridiskt kön inte skilde sig från kontrollerna för perioden 1989-2003. En förhöjd risk att ha vårdats för psykisk sjukdom kvarstod dock under hela perioden. Studien var inte designad för att avgöra om könsbekräftande behandling förbättrar utfallet men pekar på behovet av bättre omhändertagande av personer som genomgått könsbekräftande åtgärder. **Studie IV** undersökte utfallet efter genomgången könsbekräftande behandling. Uppföljningstiden var i genomsnitt (SD) 7,2 (7,3) år. Sexton män (personer som tillskrivits kvinnligt kön vid födseln) och 49 kvinnor (personer som tillskrivits manligt kön vid födseln) intervjuades. En klar majoritet rapporterade att de kände sig könskongruenta och generellt förbättrade. Trots detta var psykisk sjuklighet och tidigare självmordsförsök vanligt. Det var också vanligt att ha varit utsatt för negativa barndomsupplevelser (fysisk eller känslomässig misshandel och/eller sexuella

övergrepp) och att i vuxen ålder varit utsatt för diskriminering, trakasserier samt fysiskt och sexuellt våld. Att inte vara född i Sverige, att ha utsatts för negativa barndomsupplevelser och att inte vara accepterad i sin könstillhörighet av omgivningen var riskfaktorer för psykisk sjuklighet.

LIST OF SCIENTIFIC PAPERS

I. Berglund, H., Lindström, P., **Dhejne-Helmy, C.**, & Savic, I. (2008). Male-to female transsexuals show sex-atypical hypothalamus activation when smelling odorous steroids. *Cerebral Cortex, 18*(8), 1900-1908. doi:bhm216 [pii]10.1093/cercor/bhm216

II. **Dhejne, C.**, Öberg, K., Arver, S., & Landén, M. (2014). An analysis of all applications for sex reassignment surgery in Sweden, 1960-2010: prevalence, incidence, and regrets. *Archives of Sexual Behavior, 43*(8), 1535-1545. doi:10.1007/s10508-014-0300-8

III. **Dhejne, C.**, Lichtenstein, P., Boman, M., Johansson, A. L., Långström, N., & Landén, M. (2011). Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. *PloS One, 6*(2), e16885. doi:10.1371/journal.pone.0016885

IV. **Dhejne, C.**, Öberg, K., Arver, S., Kardell, M., Werner, S., & Landén, M. Gender congruence and psychiatric morbidity after gender-affirming health care: Relation to childhood adversities and adult stressful life events. *Manuscript.*

CONTENTS

LIST OF ABBREVIATIONS

ADHD	Attention-deficit/hyperactivity disorder
AFAB	Assigned female at birth
AMAB	Assigned male at birth
AND	4,6-androstadien-3-one
APA	American Psychiatric Association
ASRS-V1.1 screener	Adult ADHD Self-Report Scale screener
AQ	Autism Spectrum Quotient
BSTC	Bed nucleus of the stria terminalis
CI	Confidence interval
C-S	Cross-sectional
DSM	The Diagnostic and Statistical Manual for Mental Disorders
ENIGI	European Network for the Investigation of Gender Incongruence
EPATH	European Professional Association for Transgender Health
EST	Estra-1,3,5(10),16-tetraen-3-ol
FM, FTM or FtM	Female-to-male, refers to a person assigned female at birth who identifies as a man and wants to transition, is transitioning or has transitioned to a male
GAS	Gender-affirming surgery (synonymous with GCS)
GCS	Gender-confirming surgery (synonymous with GAS)
GD	Gender Dysphoria
CGI-I	Clinical Global Impression-Improvement
GID	Gender Identity Disorder
GIDAANT	Gender Identity Disorder of Adolescence or Adulthood, Nontranssexual Type
GIDNOS	Gender Identity Disorder Not Otherwise Specified
HBIGDA	Harry Benjamin International Gender Dysphoria Association
HR	Hazard ratio
HT	Hormone therapy
ICD	International Classification of Diseases and Related Health Problems

MF, MTF or MtF	Male-to-female, refers to a person assigned male at birth who identifies as a woman and wants to transition, is transitioning or has transitioned to a female
MINI	Mini International Neuropsychiatric Interview
N/A	Not applicable
NS	Not stated
OO	Different common odors
P	Prospective
PET	Positron emission tomography
R	Retrospective
rCBF	Regional cerebral blood flow
SOC	Standards of care for the health of transsexual, transgender and gender non-conforming people issued by WPATH
SCID-I	Structured Clinical Interview for DSM-IV Axis I Disorders
SRS	Sex reassignment surgery
WHO	World Health Organization
WPATH	World Professional Association for Transgender Health

1 INTRODUCTION

The word identity, from the Latin *identitas*, means "the same". It refers to a mental image of sameness with others. "Gender identity" denotes the inner sense of what gender one belongs to, the mental sameness with others of that gender (Kohlberg, 1966; Steensma, Kreukels, de Vries, & Cohen-Kettenis, 2013).

The term gender identity is a modern concept (Pfäfflin 2011). Money (1955) introduced the term "gender role" and defined it as "all those things that a person says or does to disclose himself or herself as having a status of boy or man, girl or a woman, respectively. It includes, but is not restricted to, sexuality in the sense of eroticism". With the work of psychoanalyst Stoller (1968), the cognitive developmental psychologist Kohlberg (1966), and others, gender identity became seen as something separate from gender role. Money (1994) later described it as follows: "Gender identity is the private experience of gender role, and gender role is the public manifestation of gender identity. Both are like two sides of the same coin and constitute the unity of gender identity and gender role. Gender identity is the sameness, unity, and persistence of one's individuality as male, female, or androgynous, in greater or lesser degree especially as it is experienced in self-awareness and behavior." With the introduction of gender identity as a separate concept, gender role was gradually reduced to behaviors, attitudes, and personality traits, which in a given society and historical period are typically attributed to, expected from, or preferred by persons of that gender (Huston, 1983).

Today, gender identity and gender role are seen as two among the multiple levels of sex or gender (Dhejne & Arver, 2012; Winter et al., (2016); Table 1 provides an overview. For most persons, the gender identity is in line with the gender assigned at birth, leading to feelings of gender congruence. Gender dysphoria as a symptom denotes the distress that gender incongruence may cause when the gender identity is not in line with the gender assigned at birth. If the distress is intense and gender-affirming health care is needed to adjust the primary and secondary sex characteristics, the individual may fulfill the criteria for the medical diagnosis Transsexualism (ICD-10) or Gender Dysphoria (DSM-5) (American Psychiatric Association, 2013; World Health Organization, 1992). Gender-affirming medical and surgical treatment is described in the Standards of Care version 7 (SOC 7) from the World Professional Association for Transgender Health (WPATH) (Coleman et al., 2012). In Sweden, the National Board of Health and Welfare have issued national guidelines that adhere closely to the SOC 7. Gender-affirming medical treatment aims to alter the bodily characteristics to better align with the person's gender identity and ease gender dysphoria. Examples of gender-affirming medical treatment are hormone treatment, hair removal, voice therapy, and surgery; surgery options include vaginoplasty, breast augmentation, thyroid chondroplasty surgery, pitch-raising vocal

fold surgery, chest reconstructive surgery, and phalloplasty. Fertility preservation should be offered prior to hormone treatment and genital surgery (National Board of Health and Welfare, 2015).

Table 1. Different levels of gender

Legal gender	The gender defined in legal documents and birth certificate.
Chromosomal sex	Karyotype describing the presence or absence of Y and/or X chromosomes.
Hormonal sex	Female or male sexual hormone pattern.
Anatomical sex	Female or male primary and secondary sex organs.
Gender identity	The perception of being a man, woman, or some other gender.
Gender expression	How the person expresses their gender identity in a social context with more or less well defined social gender characteristics, for example the way of dressing.
Gender role	Behaviors, attitudes, and personality traits that in a given society and historical period are typically attributed to, expected from, or preferred by persons of that gender.

For many years, gender identity was seen as binary: an individual had either a female or a male gender identity (Fraser & Knudson, 2017; Wålinder, 1968). However, others have argued that gender identity should be seen as a non-binary spectrum, where female and male gender identity are two of many gender identities that also include "non-binary", "gender fluid", "transgender", "transgender masculine", or "transgender feminine". (Beek, Kreukels, Cohen-Kettenis, & Steensma, 2015; Bockting, 2008; Cohen-Kettenis & Pfäfflin, 2010; Fisk, 1974; Fraser & Knudson, 2017; Richards et al., 2016). The non-binary model is currently reflected in SOC 7 from WPATH (Coleman et al., 2012). The author of the summary chapter acknowledges the non-binary concept and that not all gender incongruent individuals are gender dysphoric, fulfill a medical diagnosis, or need gender-affirming treatment. However, the participants in the studies included in this thesis were all gender binary with a medical diagnosis of gender dysphoria according to ICD-8, 9, or 10 (World Health Organization, 1967, 1978, 1992). Therefore, this summary chapter will mainly focus on this group.

1.1 TERMINOLOGY / LANGUAGE

The language we use reflects our underlying frames and references. During the past years, the conceptualization of gender incongruence and gender dysphoria has changed, as has the

language describing the phenomena. The main conceptual change is that among the different levels of sex and gender, the personal experience of gender identity has priority. To help eliminate stigma, prevent discrimination, and promote health in the transgender group, the use of inclusive language that promotes respect and dignity has become increasingly important (Bouman et al., 2016; von Vogelsang, Milton, Ericsson, & Strömberg, 2016). A list of definitions reflecting some of the changes of the new conceptualization is presented later in this section. The language and changes of conceptualization is an ongoing process and the definitions in Table 2 reflect the usage in early 2017.

The last years' changes in terminology are reflected in the four papers of this thesis. Two clarifications regarding the terminology in this summary chapter are necessary to avoid confusion.

First, trans/transgender man (a person assigned female gender at birth who identifies as male) or trans/transgender woman (a person assigned male gender at birth who identifies as female) will be used to describe individuals before, during, and after medical and legal transition (Reisner, et al., 2016a; Winter et al., 2016). Trans/transgender man or woman will replace the formerly used terms female-to-male transsexuals (FM, FtM, FTM) or male-to-female transsexuals (MF, MtF, MTF) (Reisner, et al., 2016a; Winter et al., 2016). However, tables and figures from already published articles will not be changed. In Study IV, a majority of the participants who were all post legal and medical transition identified themselves according with their new assigned gender. Hence, they will be described as men if assigned female gender at birth, or women if assigned male gender at birth.

Second, when referring to individuals with any of the gender dysphoria diagnoses, I included any versions of ICD-8, 9, or10 and or DSM-III-5 (American Psychiatric Association, 1980, 1987, 1994, 2000, 2013; World Health Organization, 1967, 1978, 1992).

List of definitions

Not all the definitions in Table 2 are used in this summary chapter, but they are nevertheless included to illuminate the changes in how gender incongruence and gender dysphoria have been conceptualized.

Table 2. List of definitions.

Androphilic	Sexual orientation towards men or masculinity (Reisner, et al., 2016a).
Birth-assigned sex	The sex/gender that was assigned at birth. This supersedes the term *biological sex, natal sex, or actual*

	sex. If chromosomal, gonadal, hormonal, or genital sex characteristics are discussed, these terms should be used (Bouman et al., 2016).
Cisgender person (Cis person)	A person whose gender identity matches the sex assigned at birth and who, unlike transgender people, does not experience gender incongruence (Winter et al., 2016).
Gender binary	A view that there are only two genders (girls/women and boys/men) that are separate and unchanging (Fraser & Knudson, 2017).
Gender-affirming health care /Gender-confirming health care	Medical treatments aiming to alter the bodily characteristics in order to better align with the person's gender identity and ease gender dysphoria. Examples of gender-affirming health care include hormone treatments, hair removal, voice therapy, and gender-affirming surgery (Zeluf et al., 2016).
Gender-affirming surgery /Gender-confirming surgery	Range of surgeries that create physical characteristics that are in line with gender identity, including vaginoplasty, breast augmentation, thyroid chondroplasty surgery, pitch-raising vocal fold surgery, chest surgery, and phalloplasty. Sometimes referred to as sex reassignment surgery (SRS) (Berli et al., 2017).
Gender dysphoria	Distress that gender incongruence may cause (Winter et al., 2016; Zeluf et al., 2016).
Gender Dysphoria	Refers to the diagnostic term in DSM-5 (American Psychiatric Association, 2013).
Gender Identity Disorder	Refers to the diagnostic term in DSM-IV and DSM-IV-TR (American Psychiatric Association, 1994, 2000).
Gender non-conforming	This term refers to people who do not conform to society's expectations for their gender roles or gender expression. Another term used for this is "gender-variant" (Berli et al., 2017; Coleman et al., 2012).
Gender normative	Gender roles and/or gender expression that matches social and cultural expectations (Coleman et al., 2012).

Gender transition	A person's adoption of characteristics that they feel match their gender identity. Gender transition can involve social, physical, and legal transition. Social transition includes changing appearance (including styles of dress and hair), name and pronoun. Legal gender recognition includes change of legal gender and arranging new identity documents. Physical transition can facilitate social transition and includes gender-affirming medical interventions such as hormone therapy and gender-affirming surgery (Berli et al., 2017; Winter et al., 2016).
Gynephilic	A sexual orientation towards women or femininity (Reisner et al., 2016a).
Legal gender recognition	The process by which a person's legal gender is changed to align with the person's gender identity (Zeluf et al., 2016).
Read as	Denotes how others read or perceive your gender (Vancouver Costal Health, 2016).
Sexual orientation	Describes whom one is sexually attracted to. The sexual orientation of transgender people should be defined by the individual. It is often described based on the lived gender. A transgender woman attracted to other women would be a lesbian, and a transgender man attracted to other men would be a gay man (Bouman et al., 2016; Winter et al., 2016).
Sex reassignment	Denotes the process to make a social, legal and physical gender transition (Vancouver Costal Health, 2016).
Sex reassignment surgery	See gender-affirming surgery (Vancouver Costal Health, 2016).
Transfeminine	This umbrella term describes people who were assigned male at birth, who are transgender, and whose gender expression leans towards the feminine (Zeluf et al., 2016).
Transmasculine	This umbrella term describes people who were assigned female at birth, who are transgender, and whose gender

	expression leans towards the masculine (Zeluf et al., 2016).
Transsexual	A clinical term which has historically been used to describe those transgender people who sought medical intervention (hormones, surgery) for gender affirmation. The term is less commonly used in the present day although some individuals and communities maintain a strong and affirmative connection to this term (Center of Excellence for Transgender Health, 2016).
Transgender person (Trans person)	A transgender person experiences some degree of gender incongruence. It is an umbrella term that describes a wide range of people whose gender and/or gender expression differ from their assigned sex and/or the societal and cultural expectations of their assigned sex (Berli et al., 2017; Winter et al., 2016).
Transgender man (Trans man)	Denotes someone with a male gender identity who was assigned female at birth, and is transitioning or has transitioned to male phenotype. Also known as female-to male or FtM (Berli et al., 2017; Winter et al., 2016).
Transgender woman (Trans woman)	Denotes someone with a female gender identity who was assigned male at birth, and is transitioning or has transitioned to female phenotype. Also known as male to female or MtF (Berli et al., 2017; Winter et al., 2016).
Transsexualism	A medical diagnosis in ICD-10 (World Health Organization, 1992), and DSM-III and DSM-III-R (American Psychiatric Association, 1980, 1987).

1.2 CULTARAL AND HISTORICAL REMARKS

Individuals with gender non-conforming behavior and identities have existed and still exist in many cultures and countries. Sometimes they have been seen as having special gifts such as being a shaman. Individuals assigned male at birth with gender atypical behavior or expressions are recognized as *Fa'afafine* in the Samoan Islands (Poasa, Blanchard, & Zucker, 2004), *Hijra* in India, *Maknyah* in Malaysia, *Phuying khaam phet* in Thailand, *Xanith* in Oman (Winter, 2009), *Acaults* in Myanmar (Coleman, Colgan, & Gooren, 1992), *Travesti* in Brazil (Kulic,

1998), *Two spirits* in some First Nation people in North America (Stoller, 1976), *Sarombavy* in Madagascar (Green, 1969), *Muxes* in Mexico, and *'Yan dandu* in Nigeria (Murray, 2000). Individuals assigned female at birth with gender non-conforming behavior are less common, but the polar explorer Knut Rasmussen described a powerful shaman among indigenous people of Greenland who was able to transform herself to a male (Rasmussen, 1930). In Albania, "sworn virgins" are individuals assigned female at birth who live and are accepted as males (Herdt, 1994). In Afghanistan there is a tradition to allow the youngest child – if there are no sons – to be raised as a boy until puberty, after which the child must revert to a female gender role (Nordberg, 2015).

Greek mythology and folk tales in East India include stories of cross-gender behavior and/or identity. As in the myth of Teiresias, tales often described that Gods could alter the sex of humans either as a favor or a punishment (Green, 1969). Historical descriptions include roman emperors who behaved as women or wanted to become a woman, Pope John VIII who died after giving birth to a child, and Chevalier d'Eon – a mistress to Louis XV – who lived half his life as a man and half her life as woman, to mention a few (Green, 1969).

1.3 MEDICAL BACKGROUND

The physician and founder of the German Institut für Sexualwissenschaft in Berlin, Magnus Hirschfeld (1868-1935), was the first to distinguish homosexuality (sexual attraction to individuals of the same sex) from transsexualism. The phenomenon that some individuals had a strong wish to carry the clothes traditionally belonging to the other sex he called *Transvestitismus.* He noticed a subgroup that also had a strong desire to change their sex, which was later called genuine transvestism or spiritual transsexualism (*Seelischem Transsexualismus*) (Hirschfeld, 1923). Havelock Ellis (1928) in Britain coined the term "Eonism" for the same condition, derived from the name Chevalier d'Eon. In 1949, Cauldwell (1949) used the term "Transexualism", and this was later picked up by Harry Benjamin but then spelt with a double *s*, "Transsexualism" (Benjamin 1966). The first described gender-affirming surgery took place in Germany. Abraham (1931) reported two individuals' assigned male gender at birth, both of whom had undergone castration, penectomy, and vaginoplasty (Abraham, 1931). The Danish painter Einar Wegener described the transition to Lili Elbe in her autobiography *Man into Woman* (Elbe, 1933). This story has also featured as a movie, *The Danish Girl* (2015). Lili Elbe was a patient of Magnus Hirschfelt and Kurt Warnekros. She underwent castration and penectomy and had also ovaries implanted in 1930. The following year she was legally reassigned as female. She died the same year due to complications following a uterus transplantation. A similar case from Germany was described by Huelke

(1949). Gender-affirming medical treatment did not become well known, however, until the endocrinologist Christian Hamburger presented the medical transition of Christine Joergensen. Hamburger described the psychiatric and somatic evaluation, the cross-sex hormone treatment, and the surgery performed (castration and penectomy). He also described the necessity of legal changes such as permission to wear female clothes in public, legal recognition as a woman, and the legal right to undergo castration, which was forbidden in some countries at that time (Hamburger, Stürup, & Dahl-Iversen, 1953a). Christine Joergensen become well known, and later the same year Hamburger reported that he received letters from 465 patients (76% of whom had been assigned male at birth) from all over the world applying to undergo treatment (Hamburger, 1953b). Later reports from Stockholm and Oslo described both assigned males (n = 8) and females (n = 8) who were treated in a similar protocol as described by Hamburger and coworkers (1953) (Anchersen, 1956; Hertz, Tillinger, & Westman, 1961; Vogt, 1968). In Casablanca, the French gynecologist George Burou developed the penile skin flap inversion vaginoplasty for transgender women in 1956, and later on operated many transgender women. He did not publish his work, but his work is described by Hage and coworkers 2007 (Hage, Karim, & Laub, 2007), and in the documentary *I am a woman now* by Michiel van Erp from 2011.

The *Transsexual phenomenon* was published in 1966 by the endocrinologist Harry Benjamin, describing what was now called transsexualism and detailing a treatment protocol for the condition, which was similar to that of Hamburger (Benjamin 1966).

Treatment programs for individuals with gender dysphoria were set up in Europe and the USA thereafter, and the Harry Benjamin International Gender Dysphoria Association (HBIGDA) – today the World Association for Transgender Health (WPATH) – was founded.

That gender dysphoria should be treated with gender-affirming medical intervention as described by Hamburger (1953) and Benjamin (1966) and not with psychotherapy was, and is sometimes still, controversial. Attitudes towards gender-affirming medical treatment among medical professionals was studied by Green and coworkers and revealed a very restrictive attitude (Green, Stoller, & Mac Andrew, 1966). Some argued that the gender-affirming treatment should be called transgender mutation and saw it as a pre-psychotic or neurotic condition that should be treated with psychotherapy, and that the outcome of gender-affirming treatment was not as positive as initially reported (Kubie & Mackie, 1968; Lothstein & Levine, 1981). The first Standards of Care (SOC) for hormonal and surgical reassignment of gender dysphoric persons was published in 1979 (Fraser & Knudson, 2017). They described the evaluation procedure, eligibility, and readiness criteria for hormone and surgery treatment. The

SOC has been updated many times and the current (2017) version is version 7 (SOC 7) (Coleman et al., 2012).

1.4 DEVELOPMENT OF GENDER-AFFIRMING HEALTH CARE IN SWEDEN

The endocrinologist Rolf Luft at Karolinska University Hospital in Stockholm and the psychiatrist Jan Wålinder at St. Jörgen's Hospital in Gothenburg introduced evaluation and gender-affirming treatment with cross-hormone and gender-affirming genital surgery as described by Benjamin (1966) (Wålinder, 1967). Gender teams or treatment centers were initially established in Gothenburg and later in Stockholm, Uppsala, Lund, Linköping, and Umeå.

Based on the work of Benjamin, Wålinder outlined diagnostic criteria for transsexualism (Wålinder, 1968) and eligibility and readiness criteria for sex reassignment (Wålinder & Thuwe, 1975).

Diagnostic criteria, Wålinder (1968):

1. A sense of belonging to the opposite sex, of having been born with the wrong sex, of being one of nature's extant errors.
2. A sense of estrangement with one's own body; all indications of sex differentiation are considered as afflictions and repugnant.
3. A strong desire to physically resemble the opposite sex and a need for gender-confirming medical treatment with cross-sex hormones and surgery.
4. A desire to be accepted by the community as belonging to the opposite sex.

Eligibility and readiness criteria for sex reassignment, Wålinder & Thuwe (1975):

1. A clear diagnosis established over at least one year, preferably two years. Onset (since early childhood), development, and symptomatology must be typical. Psychiatric observation, psychological test designed to evaluate femininity and masculinity, and exclusion of a psychiatric illness, and preferably also a period of observation in hospital should be included. Somatic causes of the symptoms must have been excluded.
2. A one-year period of social transition prior to gender-affirming treatment.
3. Personal and emotional stability, good intellectual capacity, and the absence of signs of psychotic reaction in order to cope with the transition.
4. Physical build, voice, hair growth etc. should "be such that the transsexual will not appear too conspicuous".
5. Other forms of treatment are either not possible or have no prospect of success.

6. A stable social situation.
7. A continuous contact with the gender team during the treatment period.

A history of cross-dressing, late onset, and not being able to be read as a woman or a man were removed as contraindications to sex reassignment in the eighties following the results of a study by Lundström (1981). He conducted a follow-up study of 31 (5 assigned females and 26 assigned males at birth) cases who were not accepted for sex reassignment 1962-1974. The reasons for non-acceptance were that they either did not fulfill the diagnostic criteria defined by Wålinder (1968) (due to conditions bordering to homosexuality or transvestism) or the requirements for sex reassignment (due to low intensity of symptoms or psychosocial instability). Lundström found that seven individuals had undergone or commenced transition at other clinics, and only five out of thirty-one were satisfied with their situation. The remaining individuals still felt gender incongruent, had gender dysphoria, and wanted a legal and medical transition. One had committed suicide. Lundström concluded that gender dysphoria that had originated in the teenage period or later also seemed (with few exceptions) to persist, just as for early onset gender dysphoria. Furthermore, individuals with compulsive cross-dressing had great difficulty reconciling themselves with the sex assigned at birth (Lundström, 1981).

Development of endocrine treatment

The first structured guidelines in Sweden for endocrine therapy were presented in 1995. Prior to that, most patient care was provided by physicians especially interested in the patient group and often in addition to other clinical duties. In the latter part of the 1990s, care gradually became more structured, and was provided at six university hospitals. Contemporary endocrine treatment reflects availability and development of pharmaceutical forms, dosing, and types of molecules. The most commonly used hormone replacement therapy in females was conjugated estrogen from pregnant mares.

Development of surgical treatment

Regarding surgical treatment, until 1986 transgender women underwent either castration or received a neovagina ad modum McIndoe (a split thickness skin graft that was used to line the wall of the vagina); thus a neoclitoris was not constructed. The penis flap technique with a construction of a neoclitoris has been used since 1986. Transgender men underwent a mastectomy and hysterosalpingo-oophorectomy. For those who underwent phalloplasty, an abdominal flap was used prior to 1986, and thereafter a pedicled groin flap (Eldh, Berg, & Gustafsson, 1997).

Development of voice therapy

Swedish speech and language pathologists and phoniatricians developed voice therapy at an early stage and Eva Söderpalm published Transsexualism from a speech and language perspective (Söderpalm 1996).

Development of informal national guidelines for transgender health care

Over the years, informal national guidelines were developed. Individuals presenting with gender dysphoria were referred to one of six specialized gender teams at psychiatric clinics. The national guidelines included approximately one year of diagnostic evaluation by a psychiatrist, a psychologist, and a social worker. Gender binary individuals diagnosed with Transsexualism according to ICD-10 were encouraged to start social transition and were then referred for gender-affirming treatment. After approximately two years of evaluation and treatment, the person could apply to the Legal Board of the National Board of Health and Welfare in order to receive permission for gender-affirming genital surgery and a change of legal sex status. A medical certificate based on the evaluation process accompanied the application. Until 1990, it was common with a two-step procedure where the initial application was for name change and sterilization. The second application was for final permission to undergo juridical gender reassignment and to obtain permission for gender-confirming genital surgery (Dhejne, Öberg, Arver, & Landén, 2014).

Evaluation and treatment of today

Evaluation and treatment adhere since 2015 to the National guidelines "Good care of adults with gender dysphoria" published by the National Board of Health and Welfare. The main changes were: (1) a more flexible and individualized evaluation process; (2) that gender-confirming medical treatment should not be reserved for transgender persons who fulfill the criteria of Transsexualism, but could also be offered to those with "other gender identity disorders" and "unspecified gender identity disorder"; (3) fertility preservation should be offered to patients prior to gender-confirming medical treatment; and (4) facial feminization surgery and hip liposuction could be offered in some cases. The guidelines also emphasize the importance of working in multidisciplinary teams (The National Board of Health and Welfare, 2015).

Below is an overview of gender-affirming treatment included in Swedish state-subsidized health care of today (The National Board of Health and Welfare, 2015).

Masculinizing hormone treatment is administrated either as testosterone undecanoate (a long-acting ester) or testosterone enanthate injected intramuscularly every 12 weeks. Transdermal testosterone gels are an alternative, and are preferred by some patients despite the inconvenience of daily application (National Board of Health and Welfare, 2015).

Masculinization surgery consists of a bilateral mastectomy and chest contouring, and a hysterectomy and hysterosalpingo-oophorectomy. For phallus reconstruction, either a free anterolateral thigh flap (ALT), or metaoidioplasty is used. In metaoidioplasty, the surgeons use the clitoris (which is enlarged by testosterone) for the reconstruction. Further hip liposuction should be offered (National Board of Health and Welfare, 2015).

Feminization hormone treatment favors the use of transdermal estradiol administration, though injections and oral preparations are also used. Synthetic derivatives are avoided because they seem to carry an increased risk for thrombosis. Gestagens have been a part of treatment not least due to their anti-androgenic effects. Medroxyprogesterone and the more potent cyproterone acetate are still being used despite side effects such as depression and hyperprolactinemia (National Board of Health and Welfare, 2015).

Feminization surgery, thyroid chondroplasty surgery, is offered, as well as pitch-raising vocal fold surgery f voice therapy is insufficient. Regarding vaginoplasty genital surgery, the most common technique is the use of solely penile skin to create the intra-vaginal lining in a two-step procedure. Skin grafts and large bowel segments are rarely used for vaginal lining (Eldh et al., 1997). Facial feminization surgery has been performed in some cases since 2015 (Lundgren et al., 2016).

Voice therapy is offered to all transgender women, and the treatment has been the subject of research (Söderpalm, Larsson, & Almquist, 2004). Transgender men are offered voice therapy if needed; the effect of testosterone on the vocal folds and satisfaction with the voice has recently been studied (Nygren, Nordenskjöld, Arver, & Södersten, 2016).

Hair removal by electrolysis or intense pulsed light (IPL) is also included for transgender women (National Board of Health and Welfare, 2015).

1.5 LEGAL GENDER RECOGNITION

Due to the work of Jan Wålinder, Inga Thuwe, and Rolf Luft, Sweden became in 1972 the first country in the world where it was possible to legally change gender. The law regulated not only legal gender recognition but also permission to undergo gender-affirming genital surgery (Wålinder & Thuwe, 1976).

During the time period relevant to this thesis, the law stated that a person could obtain permission for gender-confirming genital surgery and change of legal sex if:

1. The person since youth had felt that she/he belongs to a sex other than that recorded on the birth certificate.
2. The person had lived for a considerable time in accordance with this new gender role.
3. The person is anticipated to continue to live in such a gender role.
4. The person is at least 18 years old, a Swedish citizen, unmarried, and sterile. Not stated in the law but implicit due to the sterilization requirement was also a requirement of gender-affirming genital surgery, i.e., vaginoplasty for transgender women and at least hysterectomy for transgender men.

Gradual changes in praxis have for the last 35 years enabled late onset gender dysphoric individuals to be eligible.

Legal changes since 2013

As of 2013, the requirement of being sterile and unmarried was removed, and it is now sufficient to have permanent residency in Sweden. After changes to the law, fertility preservation is offered prior to treatment and the implicit requirement for gender-affirming genital surgery was also removed. The Discrimination Act protecting against discrimination in many areas, including healthcare, now also includes gender identity or expression as a ground for discrimination.

1.6 CLASSIFICATION

Harry Benjamin suggested in his book The Transsexual Phenomenon a means to classify persons with gender identity conflict and or cross-gender expression (Benjamin 1966). For assigned males at birth, he identified transvestites of three types: I) pseudo-transvestites, II) fetishistic transvestites, and III) true transvestites. He distinguished these from transsexuals of three types which he termed type IV) non-surgical transsexuals, V) moderate intensity transsexuals, and VI) high intensity transsexuals. Wålinder (1968) developed the work of Benjamin.

The criteria from Wålinder (1968) and Benjamin (1966) consist of three core criteria for gender incongruence/gender dysphoria:

Core criteria for gender incongruence/gender dysphoria

1. Intrapersonal gender incongruence, a gender identity not in line with the assigned sex at birth.
2. Social gender incongruence, the need for the gender identity to be accepted and confirmed by others.
3. Body dysphoria, with different degrees of avoidance and or repulsion to the physical characteristics of the assigned gender at birth. When body dysphoria is severe, there is a need and a wish for gender-affirming medical treatment to adjust the physical characteristics in order to be more congruent with the gender identity.

The three core criteria for gender incongruence/gender dysphoria with or without distress or impairment criteria have formed diagnostic criteria in both ICD (World Health Organization, 1978, 1992) and DSM (American Psychiatric Association, 1980, 1987, 1994, 2000, 2013).

Subcategorization

It has long been recognized that persons with gender dysphoria represented a heterogeneous group and differed regarding sexual interest, sexual orientation, history of cross-dressing or not, and age of onset of gender dysphoria (Benjamin 1966; Fisk, 1974; Hirschfeld, 1923; Wålinder, 1967). The different clinical presentations raised the question of whether there were different backgrounds and causes of gender incongruence/gender dysphoria. Subcategorization was also driven by the need to find the right candidates for gender-affirming treatment and especially gender-affirming genital surgery. Who would benefit the most, and not regret the procedure (Wålinder, Lundström & Thuwe 1978)? The descriptions and theories around the different subcategories have mainly concerned transgender women. Over the years, different ways to subcategorize have been proposed.

Subcategorization based on psychodynamic background

Person and Ovesey suggested two groups, primary and secondary transsexualism (Person & Ovesey, 1974a, 1974b). Primary transsexualism was also called "true" (Dolan, 1987) or "core" transsexualism (Lundström, Pauly, & Wålinder, 1984). They were described as persons with a cross-gender identity since early childhood, a strong repulsion towards their genitals, and sexual orientation towards their assigned sex at birth. They had a low libido or were asexual,

and had no history of cross-dressing for sexual purposes. Furthermore, they applied for gender-affirming medical treatment at a young age. Most transgender men were seen as belonging to this group, but only some of the transgender women (Landén, 1999).

The cross-gender identity and gender dysphoria of persons with secondary transsexualism started in puberty or later. The libido was normal. They had less or no repulsion towards their genitals and their gender dysphoria fluctuated. Secondary transsexualism has been subdivided into a condition bordering on transvestism and a condition bordering on homosexuality. The group bordering on transvestism had a history of cross-dressing starting around puberty and initially linked to sexual purposes. Later on, the sexual excitement diminished and cross-dressing was more for emotional comfort. They were sexually attracted to women. The group bordering on homosexuality were instead sexually attracted to men and had no history of cross-dressing (Landén, 1999; Lundström, 1981)

Person and Ovesey (1974a, 1974b) suggested that primary and secondary transsexualism had different etiological backgrounds. Secondary transsexualism was seen as a regressive phenomenon developed by homosexual or transvestic individuals under conditions of stress. Primary transsexualism was different and had another psychodynamic background.

Subcategorization based on sexual orientation

Wålinder (1967) described in his initial work three groups of transsexualism: homosexual, heterosexual, and asexual.

Blanchard developed that further and introduced a classification based on sexual orientation (in relation to assigned sex at birth). He described gender dysphoria of homosexual or non-homosexual type (Blanchard, 1985, 1989). The homosexual group included both assigned males and females at birth who were exclusively attracted to males or females, respectively. He defined the other group as non-homosexual. Non-homosexual transgender women were seen as having a transvestic disorder or autogynephilia. Autogynephilia denotes the sexual attraction assigned men at birth could have towards the thought or image of themselves as a woman (Blanchard, 2005; Lawrence, 2011).

Subcategorization based on age of onset for gender dysphoria

Gender dysphoria can also be subcategorized according to age of onset. The definition of early versus late onset varies (Cohen-Kettenis & Pfafflin, 2010; Zucker, Lawrence, & Kreukels, 2016). Some defined early-onset transsexualism as: “someone aware of transsexual feelings before the age of twelve” and late onset as all others (Burns, Farrell, & Brown, 1990; Doorn, Poortinga, & Verschoor, 1994; O'Gorman, 1982). The European Network for the Investigation

of Gender Incongruence (ENIGI) group has defined early onset as when someone retrospectively would have fulfilled the criteria for Gender Identity Disorder for Childhood (DSM-IV) (Nieder et al., 2011).

Debate regarding subcategorization

There has been criticism of both subcategorization per se and the categories used. Age of onset has been questioned for not being well defined, not a good predictor for clinical outcome studies, or not being useful for studies elucidating causal mechanism (Lawrence, 2010; Smith, Junger, Derntl, & Habel, 2015; Zucker et al., 2016). Using sexual orientation as an outcome predictor has on the other hand been criticized by Nieder and colleagues (2016) (Nieder, Elaut, Richards, & Dekker, 2016), who found a correlation with outcome in only one (Wierckx et al., 2014) of ten reviewed studies. Nieder and coworkers (2016) also argue that reports have shown that sexual orientation per se is fluid and unstable in transgender persons (Auer, Fuss, Hohne, Stalla, & Sievers, 2014; Cerwenka et al., 2014). The different typologies of gender dysphoria were used to evaluate who would benefit from gender-affirming genital surgery. To be seen as early onset and homosexual according to assigned sex at birth were initially necessary to be eligible for gender-affirming health care (Fisk, 1974; Wålinder, 1968). This is no longer the case, but the fear of not being seen as a candidate for gender-affirming treatment and a resistance against subcategorization still exists in the transgender community discourse (Stryker, 2008). In a Finnish study on post-medical transition, 44% reported that they falsified their story during assessment (Pimenoff & Pfäfflin, 2011). Hence, the reliability of data both regarding age of onset and sexual orientation has been questioned (Cohen-Kettenis & Pfafflin, 2010; Nieder et al., 2016).

1.7 DIAGNOSES

The term “diagnosis” is derived from the Greek meaning “through knowledge”, and is the identification of an illness or disease. Diseases can be classified on three different levels: symptomatic level, pathogenic level, and an etiological level (Wulff, Andur Pedersen, & Rosenberg, 1990). The diagnosis of gender dysphoria is so far based on the clinical presentation and symptoms (Landén, 1999). The international classification of diseases and related health problems (ICD) is a medical classification issued by the World Health Organization (WHO). It contains codes for diseases, signs and symptoms, abnormal findings, complaints, social circumstances, and external causes of injury or diseases. It is used to classify diseases for epidemiologic, statistic, diagnostic, and etiologic purposes (World Health Organization, 1992).

ICD

ICD is updated regularly and the eleventh revision (ICD-11) is scheduled to be published in 2018 (Reed et al., 2016). A gender dysphoria diagnosis first appeared in ICD-8 (World Health Organization, 1967) where it was labeled Transvestitism. The interpretation of this diagnosis is unclear and it should be remembered that Hamburger used it when he presented the treatment of Christine Joergensen (Drescher, Cohen-Kettenis, & Winter, 2012; Hamburger et al., 1953; World Health Organization, 1967). With ICD-9, the spelling was changed to Transvestism and defined as a sexual deviation in which sexual pleasure is achieved by dressing in clothes of the opposite sex. A new diagnosis also appeared: Trans-sexualism (302.5), probably reflecting the growing research following on from Harry Benjamin's work in 1966 (World Health Organization, 1978). ICD-10 included five diagnoses (Table 3) (World Health Organization, 1992). Dual Role Transvestism and Gender Identity Disorder of Childhood were omitted from the Swedish version of ICD-10 in 2009. For an overview of gender dysphoria diagnoses in the different revisions of ICD see Table 3.

Diagnostic criteria for Transsexualism, F64.0, ICD-10 (World Health Organization 1992):

1. A desire to live and be accepted as a member the opposite sex, usually accompanied by a sense of discomfort, or inappropriateness of, with one's anatomic sex and wish to have hormonal treatment and surgery to make one's body as congruent as possible with the preferred sex.
2. The transsexual identity should have been persistently present for at least 2 years.
3. It should not be symptom of another mental disorder or associated with any intersex, genetic or chromosome abnormality.

DSM

The Diagnostic and Statistical Manual for Mental Disorders (DSM) issued by the American Psychiatric Association (APA) is a parallel diagnostic classification for psychiatric diagnoses, mainly used in the United States of America and in some other countries. DSM-III was the first version that gained international approval. The idea was to use scientifically or evidenced-based medical knowledge and define diagnoses with a set of symptom criteria (American Psychiatric Association, 1980). DSM is also updated regularly and the fifth version, DSM-5, was published in 2013 (American Psychiatric Association, 2013). The criteria for gender dysphoria have varied across versions but all revolved around the core criteria of intrapersonal gender incongruence, social incongruence, and body dysphoria. DSM-III-R also introduced a new diagnosis: Gender Identity Disorder of Adolescence or Adulthood, Nontranssexual Type (GIDAANT), reflecting back to Benjamin's Type IV, non-surgical transsexuals. GIDAANT

describes individuals with gender dysphoria who would not benefit from gender-affirming genital surgery (American Psychiatric Association, 1987). Table 4 shows an overview of the different versions of DSM diagnoses.

Table 3. Gender dysphoria diagnoses in ICD.

Time period for use in Sweden	ICD version	Chapter: Parent category:	Diagnostic name
1969-1986	ICD-8 (WHO 1967)	Chapter: Psychiatric Parent category: Sexual deviation	302.3 Transvestitism
1987-1996	ICD-9 (WHO 1978)	Chapter: Psychiatric Parent category: Sexual deviation	302.3 Transvestism 302.5 Transgender-sexualism[1]
1997-ongoing	ICD-10 (WHO 1992)	Chapter: Psychiatric Parent category: Gender Identity Disorder	F64.0 Transsexualism F64.1 Dual role transgendervestism[2] F64.2 Gender Identity Disorder of childhood[2] F64.8 Other gender identity disorders F64.9 Gender Identity Disorder unspecified
2018 planned	ICD-11 proposed (Reed 2016)	Chapter: Conditions related to sexual health	Gender incongruence in adolescent or adults Gender incongruence in children

[1] Not used in Swedish version of ICD 9. [2] Not used in Swedish version of ICD 9 since January 1, 2009.

Table 4. Gender dysphoria diagnoses in DSM.

Year	DSM version	Section	Diagnostic name	Specifiers	Exclusion criteria
1980	DSM-III	Psychosexual disorders	302.5xTranssexualism 302.6 Gender Identity Disorder of Childhood (GIDC) 302.85 Atypical gender identity disorder	Sexual orientation	Disorder of sexual development /intersex Schizophrenia
1987	DSM-III-R	Disorders usually first evident in infancy, childhood or adolescence	302.50 Transsexualism 302.60 GIDC 302.85 Gender Identity Disorder of Adolescence or Adulthood, Nontranssexual Type (GIDAANT) 302.85 Gender Identity Disorder Not Otherwise Specified (GIDNOS)	Sexual orientation	0
1994	DSM-IV and DSM-IVTV	Sexual and gender identity disorders	302.85 Gender Identity Disorder in adolescents or adults (GID) 302.6 GIDC 302.6 Gender Identity Disorder Not Otherwise Specified (GIDNOS)	Attracted towards males, females, both, neither, unspecified	Disorder of sexual development/ intersex for GID but not for GIDNOS
2000	DSM-5	Gender dysphoria	302.85 Gender Dysphoria in adolescents or adults 302.6 Gender Dysphoria in children 302.6 Other specified gender dysphoria 302.6 Unspecified gender dysphoria	Post-transition With or without disorder of sexual development	0

Should gender dysphoria be a diagnosis?

It has been a subject of debate whether Transsexualism or Gender Dysphoria should be a diagnosis, and if so, whether it should be placed within the psychiatric chapter of the International Classification of Disease (World Health Organization, 1992) and in DSM (American Psychiatric Association, 2013). The first appearance of these diagnoses as psychiatric diagnoses in the aforementioned publications (using different terms) may be related to the social and medical attitudes at a time when Harry Benjamin started to describe and treat transgender persons (Drescher et al., 2012). Whether incongruence with one's gender is a natural variation or pathology, and how the different views may influence discrimination, stigma, and access to medical treatment, is well discussed in a paper by Meyer-Bahlburg (2010). The tradeoff is to reduce stigma while securing access to health care for those in need, since in most countries a diagnosis is needed in order to access gender-affirming medical treatment (Drescher, 2013; Reed et al., 2016). In order to secure access to health care, a few practitioners who partly followed the pressure of their patients argued for inclusion of a diagnosis in DSM-III in the 1970s (Pfäfflin, 2011). There was on the other hand a lot of effort made to remove the gender dysphoria diagnosis from DSM-5 in order to reduce stigma (Pfäfflin, 2011). The dual ambitions of increasing access to health care while reducing stigma and discrimination have been a major focus recently, as reflected in the WHO proposal for the next edition of the ICD (ICD-11). It is suggested that the current diagnostic term, "Transsexualism" will be replaced with "Gender Incongruence of adolescence and adulthood" and be moved from Chapter 5 (Mental and Behavioral chapter) to a new chapter entitled "Conditions Related to Sexual Health" (Reed et al., 2016).

Gender incongruence of adolescence and adulthood ICD-11 proposal

The diagnostic requirements include the continued presence for at least several months of at least two of the following:

1. A strong dislike or discomfort with the primary or secondary sex characteristics due to their incongruity with the experienced gender.
2. A strong desire to be rid of some or all of one's primary or secondary sex characteristics (or in adolescence, anticipated secondary sex characteristics).
3. A strong desire to have the primary or secondary sex characteristics of the experienced gender.
4. A strong desire to be treated (to live and be accepted) as a person of the experienced gender.

The ICD-11 proposal supports the view of many that a diagnosis describing transgender individuals should not be part of a psychiatric category but at the same time enable access to health care. However, by doing so, it also raises questions concerning the future role of mental health professionals in transgender care (Bockting, 2016a; Dhejne, Van Vlerken, Heylens, & Arcelus, 2016; Fraser & Knudson, 2017; Selvaggi & Giordano, 2014). Furthermore, a more inclusive diagnosis would decrease the possibility of using the diagnosis as a tool for epidemiology statistics and in the search for the causes of gender dysphoria (Smith et al., 2015; Zucker et al., 2016).

1.8 EPIDEMIOLOGY

Incidence denotes the frequency by which new cases of illness, injury, or other health conditions occur in a given population during a specified period (Rothman, 2002).

Prevalence is the number or proportion of cases (numerator) or events among a given population (denominator) at a given time (Rothman, 2002).

Information on incidence, prevalence, and sex ratio of individuals diagnosed with gender dysphoria diagnoses is important for planning health services. Knowledge of incidence and prevalence for a condition could also be used to formulate and test etiological hypotheses.

Incidence, prevalence, and sex ratio of transsexualism / gender dysphoria

The incidence, prevalence, and sex ratio of individuals with any of the gender dysphoria diagnoses are often calculated based on data collected for individuals in a given area who during a specific time period received a diagnosis and/or applied for gender-affirming treatment and/or change of legal gender at a clinic or to state authorities. A meta-analysis of 12 studies found the overall prevalence of transsexualism to be 1 in 21,739 individuals. If separated by gender, the figures were 1 in 14,705 assigned males at birth and 1 in 38,461 assigned females at birth. This corresponded to 2.6 transgender women to every transgender man (Arcelus et al., 2015). Included studies measured help-seeking individuals with a gender dysphoria diagnosis or subjects who applied for change of legal gender due to a gender dysphoria diagnosis. Two population-based studies have assessed the prevalence for Transsexualism (DSM-III) irrespective of help-seeking behavior. They showed a higher prevalence and a reverse sex ratio compared to the meta-analysis. In Iceland the lifetime prevalence for transgender men was 1:500 (0.2%) and zero for transgender women (Stefánsson, Líndal, Björnsson, & Guðomundsdóttir, 1991). In Taiwan, the lifetime prevalence for transgender men was 1:250 (0.4%) in small town areas and 1:1429 (0.07%) in metropolitan areas; for transgender women the prevalence was 1:2500 (0.04%) in metropolitan areas (Hwu, Yeh, & Chang, 1989). There

were no transgender women outside the metropolitan area. An overview of incidence prevalence and sex ratio studies is presented in Table 5.

The Swedish incidence, prevalence and sex ratio during the period 1960-2010 is addressed in this thesis (Study II).

Swedish studies on incidence and sex ratio of gender dysphoria

Wålinder (1971) calculated the Swedish incidence and sex ratio of all gender dysphoria diagnoses in 1968, 1969, and 1970 by asking psychiatrist colleagues how many patients they had and included his own clinic. Since then, the incidence in Sweden has been calculated by using the applications for change of legal gender and permission to undergo gender-affirming genital surgery to The National Board of Health and Welfare. This could be used as a proxy for any gender dysphoria diagnoses since a psychiatric evaluation statement must accompany the application to confirm a gender dysphoria diagnosis. The incidence increased from 0.17/100,000/year between 1972 and 1992, to 0.24/100,000/year between 1992 and 2002 (Landén, Wålinder, & Lundström, 1996; Olsson & Möller, 2003). The increase was significant for the whole group and for transgender women, but not for transgender men. Accordingly, the sex ratio changed from 1:1.4 to 1:1.8 in the period 1972-2002 (Olsson & Möller, 2003). The mean (SD) age at application for transgender women increased from 32.2 (9.5) years during 1976-1992 to 36.5 (11.0) years during 1992-2002, but was stable for transgender men during the same periods, 29.3 (7.4) and 30.0 (9.4) years, respectively (Olsson & Möller, 2003).

Table 5. Incidence, prevalence, and sex ratio of individuals with a gender dysphoria diagnosis in various locations.

Author	Location	Year or time period	Incidence /100,000 /year	Prevalence TM	Prevalence TW	Sex ratio TM:TW	Diagnosis /according to	Source of numerator	Popu-lation
Pauly (1968)	USA	1968	NS	1:400,000	1:100,000	1:4	NS	Request GCS	Total
Wålinder (1968)	Sweden	1965-1967	NS	1:103,000	1:37,000	1:2.5	Transsexualism/ Wålinder (1968)	Survey of psychiatrists	≥15 y
Wålinder (1971)	Sweden	1967-1970	0.15 total	NS	NS	1:1	Transsexualism/ Wålinder (1968)	Referral to gender clinic	≥15 y
Hoenig & Kenna (1974)	England and Wales	1958-1968	0.17-0.26 total	1:108,000	1:34,000	1:2.9	Transsexualism/ Wålinder (1968)	Referral to gender clinic	≥15 y
Sørensen & Hertoft (1980)	Denmark	1970-1977	0.21 Total 0.11 TM 0.31 TW	NS	NS	1:2.8	Transsexualism/ Wålinder (1968)	Request GCS	≥15 y

Ross et al. (1981)	Australia	1976-1978	0.58 total	1:150,000	1: 24,000	1:6.1	Transsexualism /Wålinder (1968)	Survey of psychiatrist	≥15 y
Sørensen & Hertoft (1982)	Denmark	1951-1981	NS	NS	NS	1:3.6	Transsexualism/ Wålinder (1968)	Receipt GCS	≥15 y
O'Gorman (1982)	Northern Ireland	1968-1981	NS	1:100,000	1:35,000	1:3	Transsexualism / NS	Referral to gender clinic	≥15 y
Dixen et al. (1984)	USA	1967-1979	NS	NS	NS	1:1.7	NS / NS	Request GCS	≥15 y
Blanchard et al. (1987)	Canada	1980-1984	NS	NS	NS	1:1.7	Gender dysphoric/ NS	Referral to gender clinic	≥16 y
Godlewski (1988)	Cracow, Poland	1974-1980	NS	NS	NS	5.5:1	Transsexualism / DSM-III	Referral to gender clinic	NS
Eklund et al. (1988)	The Netherlands	1976-1986	NS	1:4,000	1:8,000	1:3	NS	Receipt HT at gender clinic	≥15 y
Tsoi (1988)	Singapore	Alive 1986	NS	1:8,300	1:2,900	1:3	Transsexualism / DSM-III	Request GCS	≥15 y
Hwu et al. (1989)	Taiwan	1982-1986	NS	1:1,250 metropol. area 1:250 small town 1:1,427 rural area	1:2,500 metropol. area 0 small town and rural area	10:1 metropol.	Transsexualism / DSM-III Diagnostic Interview Schedule (DIS)	Multistage random sampling in the Taiwanese population	≥18 y
Stefansson et al. (1991)	Iceland	1931-1986	NS	1:500	0	N/A	Transsexualism / DSM-III Diagnostic Interview Schedule (DIS	505 of the birth cohort 1931 in Iceland	N/A
Bakker et al. (1993)	The Netherlands	1986-1990	NS	1:30,400	1:11,900	1:2.5	Transsexualism / Wålinder (1968)	Receipt HT	≥15 y
De Cupyere et al. (1995)	Belgium	1986-1994	NS	NS	NS	1:1.7	Transsexualism / NS	Referral to gender clinic	≥15 y
Landén et al. (1996)	Sweden	1972-1992	0.17 total	NS	NS	1:1.4	Transsexualism / Wålinder (1968), ICD-8-9	Request for GCS and change of legal gender marker	≥15 y
van Kesteren et al. (1996)	The Netherlands	1975-1992	NS	1:30,400	1:11,900	1:3	Gender dysphoric/ NS	Referral to gender clinic	Total
Weitze & Osburg (1996)	West Germany	1981-1990	0.24 total	1:94,000	1:36,000	1:2.3	NS /NS	Request for change of legal gender marker.	NS
Wilson et al. (1999)	Scotland	Circa 1998	NS	1:52,100	1:12,800	1:3.8	NS/ NS	Receipt HT and/or GCS	≥15 y
Garrels et al. (2000)	Germany	1970-1998	NS	NS	NS	1:1.9	NS/ NS	Referral to gender clinic	NS
Olsson & Möller (2003)	Sweden	1992-2002	0.24 total	NS	NS	1:1.9	Transsexualism / Wålinder (1968), ICD-8-10	Request for SCS and change of	≥15 y

								legal gender marker	
Dulko & Imielinski (2004)	Poland	NS	NS	NS	NS	3.4:1	Transsexualism / NS	Ns	NS
Smith et al. (2005)	The Netherlands	prior to 2003	NS	NS	NS	1:1.5	NS/ NS	Receipt HT and or GCS	≥15 y
Gomez-Gil et al. (2006)	Catalonia	1996-2004	0.73 total 2000-2004	1:48,100	1:21,000	1:2.6	Transsexualism / ICD-10	Referral to gender clinic	≥15 y
Pimenoff (2006)	Finland	1993-2002	NS	NS	NS	1:1	Transsexualism / ICD-10	Request for castration	NS
De Cupyere et al. (2007)	Belgium	1985-2003	NS	1:33,800	1:12,900	1:2.43	NS/ NS	Receipt GCS	≥15 y
Veale (2008)	New Zealand	1995-2008	NS	1:22,700	1:3,600	1:6	NS/ NS	Gender change in passport	≥15 y
Vujovic et al. (2009)	Serbia	1987-2006	NS	1:44,053	1:42,918	1:1	GID/ DSM-IV-TR	Referral to gender clinic	≥18 y
Meyer zu Hoberge (2009)	Germany	1981-2000	0.34 total 0.26 TM 0.41 TW 1991-2000	1:32,050	1:18,250	1:1.5	NS/NS	Request for change of legal gender marker	NS
Gómez Gil et al. (2009)	Barcelona, Spain	2000-2006	NS	NS	NS	1:2.24	Transsexualism / ICD-10		NS
Baba et al. (2011)	Japanese region Hokkaido	2003-2010	NS	1:12,200	1:25,200	2:1	GID or transsexualism/ DSM-IV or ICD-10	Referral to gender clinic	Total
Ahmadzad-Asl et al. (2011)	Iran	2002-2009	NS	1:136,000	1:145,000	1:0.96	GID / DSM-IV-TR	Referral to gender clinic	15-44 y
Kreukels et al. (2012)	Amsterdam, The Netherlands	2009	NS	NS	NS	1:2.34	Gender dysphoric individuals/ N/A	Referral to gender clinic	≥17 y
Kreukels et al. (2012)	Ghent, Belgium	2009	NS	NS	NS	1:2.5	Gender dysphoric individuals/ N/A	Referral to gender clinic	≥16 y
Kreukels et al. (2012)	Hamburg, Germany	2009	NS	NS	NS	1.33:1	Gender dysphoric individuals/ N/A	Referral to gender clinic	≥16 y
Kreukels et al. 2012.	Oslo, Norway	2009	NS	NS	NS	1.12:1	Gender dysphoric individuals/ N/A	Referral to gender clinic	≥16 y

GCS = Gender-confirming surgery; GID = Gender Identity Disorder; GIDNOS = Gender Identity Disorder Not Otherwise Specified; GD = Gender Dysphoria; HT = Hormone therapy; N/A = Not applicable; NS = Not stated; TM = Transgender men; TW = Transgender women; VHA = Veterans Health Administration; y = years old.

1.9 CAUSES

The cause of gender incongruence/gender dysphoria remains unknown. Psychosocial factors and parental style were suggested early.

A growing body of observations indicates that gender dysphoria has a neurodevelopmental origin. Different approaches have been used to elucidate if individuals with gender dysphoria are different from cisgender individuals with respect to known sex differences between

cisgender females and cisgender males, or if any other endocrine or genetic factor predispose gender dysphoria.

It has been argued that there is a risk associated with the study of causal mechanisms of gender dysphoria. The same concerns have been raised regarding research trying to elucidate the background to sexual orientation. The argument goes that human variance could be pathologized, which could increase stigma and discrimination. But studies have in fact showed the opposite: people who believed that there was a biological cause to gender dysphoria were less transphobic (Landén & Innala, 2000).

The sex-atypical differentiation of the brain hypothesis

There are known biological differences between cisgender women and men. For example, they differ regarding sex chromosomes (XX, XY), primary and secondary sex organs, and on group level in height, and brain structures. Men have a larger brain volume even if corrected for body size (Lüders, Steinmetz, & Jäncke, 2002; Ruigrok et al., 2014; Rushton & Ankney, 2009). Men also differ from women in the proportion of white and grey matter, the central division of the bed nucleus of the stria terminalis (BSTc), and the third interstitial nucleus of the anterior hypothalamus (INAH3) (Byne et al., 2000; Cosgrove, Mazure, & Staley, 2007; Lüders et al., 2002). There are also sex differences in brain function and brain chemistry. Cisgender women and men differ in aspects such as brain activation during cognitive tasks (Bell, Willson, Wilman, Dave, & Silverstone, 2006; Frings et al., 2006) and there are gender-specific differences in serotonergic and dopaminergic markers; for an overview see Cosgrave et al. (2007). Cisgender men and women have also shown different hypothalamic activation after smelling odorous sex hormone-like compounds (4,6-androstadien-3-one (AND) and oestra-1,3,5(10), 16-tetraen-3-ol (EST)). Dutch studies have shown that transgender women had female-typical hypothalamic nuclei (Kruijver et al., 2000; Zhou, Hofman, Gooren, & Swaab, 1995).

The sex differentiation of the genitals and the brain is believed to be driven by prenatal sex hormones and genetic factors (Davies & Wilkinson, 2006; Hines, 2011). Similar factors are believed to be involved in causing incongruence between the sex differentiation of the brain, and the sex differentiation of the genitals and phenotype. This is theoretically possible because the sex differentiation of the genitals occurs prior to the sex differentiation of the brain (Bao & Swaab, 2011; Savic, Garcia-Falgueras, & Swaab, 2010). According to this model, transgender women would have an under-masculinized or feminized brain and vice versa.

Sex dimorphic neural structures and functions

Following studies in the Netherlands by Kruijver et al. (2000) showing that untreated transgender women had female-typical hypothalamic nuclei, other studies have been carried out on sex dimorphic structures, neural structures, and functions.

In summary, the results are inconsistent. Some studies have shown that hormone-untreated transgender women and transgender men neurobiologically resemble the sex congruent with their gender identity or position themselves in an intermediate position (Hahn et al., 2015; Junger et al., 2014; Junger et al., 2013; Kranz et al., 2014; Lin et al., 2014; Rametti et al. 2011a, 2011b). Other studies report that transgender women and transgender men resemble their assigned sex at birth (Savic & Arver, 2011; Zubiaurre-Elorza et al., 2013). For an overview, see Smith et al. (2015).

Whether or not transgender women differ from cisgender females and/or males regarding cerebral activation on exposure to steroid odorous compounds is examined in Study I.

Sex dimorphic neural function – Pheromones

Pheromones according to the definition of Karlson and Luscher in (1959) are "substances secreted externally by an individual and perceived by an individual of the same species in which a specific response is induced, for example a specific form of behavior or process of development". The pheromonal stimulation elicits an unconscious response in contrast to the olfactory stimulation that triggers a conscious response. The pheromones have been identified in all animals including mammals. Their effect is mediated by the vomeronasal organ (VNO), but in some animals, such as pigs and ferrets, they can also be mediated by the olfactory pathway (Marazziti et al., 2011; Savic, Berglund, Gulyas, & Roland, 2001) So far, there is not enough evidence to confirm whether they exist in humans (Wyatt, 2015). However, two substances, 4,6-androstadien-3-one (AND) a testosterone derivate produced in human axillary secrete, and estra-1,3,5(10), 16-tetraen-3-ol (EST) a substance similar to estrogen, have been suggested as putative candidates for human pheromones (Marazziti et al., 2011; Savic et al., 2001). In females, the anterior hypothalamus, especially the preoptic area and ventromedial nucleus, have been shown to be activated by smelling AND, as measured by regional cerebral blood flow (rCBF) with positron emission tomography (PET). EST on the other hand only activated the olfactory regions, which were not activated by AND. In males the response was contrary, where EST activated hypothalamus more specifically in the dorsomedial and paraventricular nucleus and AND activated the olfactory regions (Savic et al., 2001).

Homosexual cisgender men also showed a similar activation pattern to heterosexual cisgender women (Savic, Berglund, & Lindstrom, 2005).

Genetic factors

A review of twin studies regarding all gender dysphoria diagnoses found that 39.1% of monozygotic male or female twins were concordant with GID, whereas all dizygotic twins were discordant (Heylens et al., 2012). This would suggest that genetic factors are important for developing of gender incongruence/dysphoria. In search for a candidate gene which could be involved in gender dysphoria, polymorphism in genes coding for the biosynthesis or actions of sex steroids have been studied. Results are, however, inconclusive regarding associations with the androgen receptor, the two estrogen receptors, and cytochrome p450 17A, which mediates activities essential for steroid production (Bentz et al., 2008; Fernandez et al., 2014a, 2014b; Fernandez et al., 2015; Hare et al., 2009; Henningsson et al., 2005; Ujike et al., 2009).

Birth order, sibling ratios

It has been suggested that feminization in males is due to a maternal immune reaction towards a male fetus. This reaction would become stronger after each pregnancy and could cause both homosexuality and gender dysphoria in assigned males birth. Birth order and sibling ratio have been examined in androphilic transgender women, who were found to be late in birth order and have a predominance of brothers (Blanchard, Zucker, Cohen-Kettenis, Gooren, & Bailey, 1996; Bozkurt, Bozkurt, & Sonmez, 2015; Poasa et al., 2004; Tsoi, Kok, & Long, 1977; VanderLaan & Vasey, 2011). However, a study from South Korea found a predominance of older sisters (Zucker, Blanchard, Kim, Pae, & Lee, 2007). The results are more conflicting regarding transgender men. One study has shown that they were late in birth order (Gómez-Gil et al., 2011), but another study found transgender boys to be born earlier than their siblings (Zucker, Lightbody, Pecore, Bradley, & Blanchard, 1998), and two studies could not find any influence of birth order (Blanchard & Sheridan, 1992; Green, 2000). None of the above studies in transgender men found any difference in sibling sex ratio compared with controls.

Psychosocial factors

Different psychosocial theories have been suggested to explain the origin of gender dysphoria. From a psychoanalytic perspective, Person and Ovesey (1974a,b) saw gender identity conflicts as a defense mechanism against separation anxiety, early identity formation, and inner conflicts. The psychoanalytic treatment should then accordingly be directed towards denial

(Person & L. Ovesey, 1974a,b). Socarides (1970) viewed gender dysphoria as a defense action against homosexuality.

Different family dynamics or structures, such as extreme closeness to the mother or an absent mother in assigned females, were believed to cause atypical gender development. An absent father or a strong parental wish for a child of a specific sex has been proposed to interfere with the child's gender identity development and in turn cause gender incongruence and gender dysphoria (Green, 1974; Levine & Lothstein, 1981; Meyer, 1982; Stoller, 1968). No solid evidence was found when these hypotheses were tested (Cohen-Kettenis & Gooren, 1999; Zucker & Bradley, 1995). Mothers of children with gender dysphoria more often had depression and met the criteria for borderline personality disorder (Marantz & Coates, 1991; Rekers, Mead, Rosen, & Brigham, 1983). This finding could, however, also be explained by a selection bias and that such parents tend to seek help more often (Cohen-Kettenis & Gooren, 1999). Wallien et al. (2007) could not find elevated psychopathology in parents (Wallien, van Goozen, & Cohen-Kettenis, 2007). Different recalled parental rearing styles have also been discussed. Transgender men have recalled that both parents were emotionally rejecting, and perceived their mothers as more overprotective and dominant compared with non-transgender individuals. Transgender women recalled their father being more controlling and critical, and their mother being disengaged (Cohen-Kettenis & Gooren, 1999; Parker & Barr, 1982; Simon, Zsolt, Fogd, & Czobor, 2011). However, if this is a cause or effect phenomena is still under dispute (Simon et al., 2011).

Later theories have suggested that a combination of specific child and parental factors during critical early periods in the child's life led to gender incongruence/dysphoria: e.g., anxiety in the child, feminine appearance in boys, or more masculine appearance in girls, combined with parental factors such as lack of boundary setting, fear of male aggression in mothers, or psychopathology in parents (Cohen-Kettenis, Owen, Kaijser, Bradley, & Zucker, 2003; Marantz & Coates, 1991; Zucker & Bradley, 1995). However, Wallien and coworker (2007, 2008) could not confirm elevated psychopathology in parents or elevated anxiety in the child (Wallien et al., 2007; Wallien, 2008).

Some authors have suggested that child abuse experiences may be implicated in the etiology of gender dysphoria (Devor, 1994; Zucker & Kuksis, 1990), while others have argued that sexual minorities are more vulnerable to childhood abuse (Andersen & Blosnich, 2013; Corliss, Cochran, & Mays, 2002; Simon et al., 2011).

John Money proposed that imprinting during the first 2-3 years influences human gender identity. He also proposed that rearing a child as a girl or a boy would result in a corresponding respective gender identity (Money, Hampson, & Hampson, 1957). He described a pair of male

twins, one of whom was accidently castrated during circumcision at the age of 7 months. This child was then raised as a girl and, according to initial reports, had a female gender identity (Money, 1975). However, long term follow-up revealed that the "girl" experienced a problematic puberty as a female and later on transitioned to live as a man (Diamond & Sigmundson, 1997). He married and adopted a child but later sadly committed suicide. The case indicates that gender identity is unlikely to be influenced through upbringing (Diamond & Sigmundson, 1997).

1.10 MORTALITY

A large (n =1331) Dutch single center study with a mean of 18.5 years follow-up period has shown a 51% higher mortality in transgender women who had been treated with cross-sex hormones compared with the general population (Asscheman et al., 2011). The causes of death were related to suicide, acquired immune deficiency syndrome, cardiovascular disease, drug abuse, and unknown causes. Pulmonary and hematological cancers were elevated. Current, but not prior, use of ethinyl estradiol was associated with a threefold increase in death due to cardiovascular disease. In contrast, no elevated mortality was seen for transgender men (Asscheman et al., 2011). Similar findings have been reported from a large cohort from the American Veterans Health Administration, who found a higher suicide rate compared with the general population (Blosnich, Brown, Wojcio, Jones, & Bossarte, 2014). A smaller retrospective Danish register study (1978-2010) of 104 transgender persons found that 10 persons (4 transgender men and 6 transgender women) died at a mean age of 53.5 (SD = 7.3) and 53 (SD = 7.9) years, respectively (Simonsen, Hald, Kristensen, & Giraldi, 2016a). By comparison, life expectancy in Denmark was at the time 78.0 and 81.9 years for males and females, respectively. Causes of death included smoking and alcohol-related diseases (n = 4), suicide (n = 2), cardiovascular diseases (n = 2), cancer (n = 1), and ulcer (n = 1) (Simonsen et al., 2016a,b). Not only deaths due to suicide but also homicide contributed to the mortality. Transgender Murder Monitoring (TMM) is a research project by Transgender Europe (TGEU) that monitors reported murders of transgender persons in order to increase awareness and honor the lives of those who might otherwise be forgotten. TGEU reports a total of 2,264 known homicides of transgender and gender-diverse people in 68 countries worldwide between January 1, 2008 and September 30, 2016 (Transgender Europe, 2017).

Study III examined mortality following legal and surgical transition.

1.11 MENTAL HEALTH

Mental health has been examined in self-identified gender dysphoric individuals as well as in transgender persons with a gender dysphoria diagnosis recruited at transgender health care service prior to or following gender-affirming treatment, or in mixed groups pre-treatment and post-treatment. A review of studies of adult transgender persons attending different stages of treatment of gender-affirming health care at the time of assessment concluded that levels of psychopathology and psychiatric morbidity are higher than normative data or controls, but improve following gender-affirming treatment (Dhejne, van Vlerken, Heylens, & Arcelus, 2016). Interestingly, de Vries and coworkers (2011) found that a majority of gender dysphoric adolescents did not suffer from psychiatric morbidity (de Vries, Doreleijers, Steensma, & Cohen-Kettenis, 2011). The above mentioned review found that the main psychiatric diagnoses were depression and anxiety disorders, while other major psychiatric disorders such as schizophrenia or bipolar disorder were rare (Dhejne et al., 2016). The results are conflicting with regard to gender differences. Some found more psychopathology in transgender women (Claes et al., 2015; Duisin et al., 2014; Simon et al 2011) and others found no differences between the gender groups (Colizzi et al., 2015; Fisher et al., 2013; Heyelens et al 204a). Some studies used cisgender control groups (Auer et al., 2013; Davey, Bouman, Meyer & Arcelus, 2014; Duisin et al., 2014) compared with normative data (Gomez-Gil, Vidal-Hagemeijer, & Salamero, 2008; Haraldsen & Dahl, 2000; Kersting et al., 2003; Kim et al., 2006; Simon et al., 2011), or compared hormone treated or non-hormone treated transgender groups (Fisher et al., 2014; Gorin-Lazard et al., 2013), but most used no comparison group. Mental health outcomes were most often evaluated with self-report measures of psychological or psychiatric symptoms, e.g., Symptom Check List-90 (SCL-90) and Hospital Anxiety and Depression Scale (HADS). Few studies examined participants with gender dysphoria diagnoses using structured diagnostic interviews such as Mini International Neuropsychiatric Interview (MINI) or Structured Clinical Interview for DSM-IV-Axis I Disorders (SCID-I). Most of these found elevated psychiatric morbidity, mainly affective and anxiety disorders, compared with the general population (Heylens et al., 2014a; Mazaheri Meybodi, Hajebi, & Ghanbari Jolfaei, 2014a). However, two studies report rates of current psychiatric morbidity to be similar to the general population (Colizzi, Costa, & Todarello, 2014; Hoshiai et al., 2010). Though Colizzi et al. (2014) excluded participants with severe psychiatric morbidity, Hoshiani et al. (2010) found that 76% had any lifetime suicide attempt or self-injury. A Swedish study examined studied 19 transgender persons all diagnosed with Transsexualism (DSM-III-R), almost half received an Axis 1 disorder diagnosis (Bodlund, Kullgren, Sundbom, &Höjerback 1993). Landén, Wålinder & Lundström (1998a) examined a national cohort of transgender persons when they

applied for legal and surgical sex reassignment in the time frame 1972-1992 in Sweden. In this cohort, more than a third had received psychiatric treatment and 20% had a history of suicide attempts (Landén et al., 1998a). A Danish register study of 104 transgender persons who had undergone legal and surgical sex reassignment reported that 28% had a psychiatric diagnoses registered before and 22% after transition, while only 6.7% were registered both before and after transition (Simonsen et al. 2016b).

Regarding personality disorder the prevalence rates range from 4.3% (Fisher et al., 2013) to 81.4% (Mazaheri Meybodi, Hajebi, & Ghanbari Jolfaei, 2014b). The type of personality disorder varied from predominately cluster B (Hepp, Kraemer, Schnyder, Miller, & Delsignore, 2005; Madeddu, Prunas, & Hartmann, 2009; Mazaheri Meybodi et al., 2014b) to cluster C (Heylens et al., 2014a). In Sweden, Bodlund, Kullgren, Sundbom and Höjerback (1993) found that 26% fulfilled the criteria for at least one personality disorder, as compared with 17% among health care professional controls. It was common to have more than one personality disorder, and cluster B (i.e., borderline, histrionic, antisocial, and narcissistic personality disorders) was more common compared to clusters of the other personality disorders. For an overview of psychiatric morbidity in the transgender population 2000-2015, see Table 15 in Appendix.

Study III and IV examined psychiatric morbidity following legal and surgical transition.

1.12 SUICIDE ATTEMPTS AND NON-SUICIDAL SELF-INJURY

Corresponding to the high numbers of death by suicide, lifetime suicide attempts in self-identified or individuals with a diagnosis of gender dysphoria are high. In pre-treatment or in mixed pre-treatment and post-treatment groups, around 30% have attempted suicide (Marshall, Claes, Bouman, Witcomb, & Arcelus, 2016; Zucker et al., 2016). Most studies report no gender differences although Landén et al. (1998a) found suicide attempts to be more common in transgender women (23% as compared with 14% in transgender men). A reduction of suicide attempts from 29% pre-treatment to 5% post gender-affirming treatment was reported by Cuypere et al. (2006) but the reduction did not account for time at risk. Non-suicidal self-injury is less studied. Claes et al. (2015) and Davey, Arcelus, Meyer, & Bouman (2016) found a prevalence rate of 19-36% and that non-suicidal self-injury was more common compared with cisgender controls (Claes et al., 2015; Davey et al., 2016). Regarding gender differences non-suicidal self-injury seems to be more common among transgender

men compared with transgender women (Claes et al., 2015; Davey et al., 2016; Skagerberg, Parkinson, & Carmichael, 2013).

1.13 CAUSES OF MENTAL HEALTH ISSUES

The reasons for high psychiatric morbidity in transgender persons both before and after gender-affirming health care are unclear. Childhood adversities such as physical, emotional, and sexual abuse have been shown to predict psychiatric morbidity (Björkenstam, Burström, Vinnerljung, & Kosidou 2016; Chen et al., 2010; Hovens et al., 2010; Kessler et al., 2010), suicide attempts, and suicide in the general population (Bruffaerts et al., 2010; Evans, Hawton, & Rodham, 2005; Jokinen, 2015). Childhood advertises is reported to be more common in sexual minority groups (Corliss, et al, 2002), and could thus be a possible explanation also in the transgender group. Minority stress and gender-related abuse in adulthood have also been put forward as reasons for psychiatric ill health in transgender persons (Meyer, 2003). Meyer (2003) describes that the stress may be both distal processes as rejection and discrimination and proximal processes where the stress results from internalized prejudice. That minority stress and gender related abuse in the transgender population is associated with increased mental health problems have been reported (Bockting et al., 2013; Claes et al., 2015; Clements-Nolle, Marx, & Katz, 2006; Nuttbrock et al., 2012; Nuttbrock et al.,2014; Reisner et al., 2016c).

Vulnerability

Adult stressful life events

The transgender group as a whole is vulnerable with numerous reports regarding discrimination, harassment, physical abuse, sexual abuse and difficulties accessing health services or negative health care encounters (Lombardi Wilchins, Priesing, & Maluf, 2002; Prunas et al., 2016; Public Health Agency of Sweden, 2015, von Vogelsang et al., 2016; Zeluf et al., 2016).

Childhood adversities

Few studies have surveyed the prevalence of childhood adversities (CA) in individuals applying for gender-affirming health care or diagnosed with a gender dysphoria diagnosis. One study found that transgender women reported a higher prevalence of emotional abuse and neglect in comparison with psychiatric inpatients (Kersting et al., 2003), and transgender women maltreated in childhood displayed worsened mental health as measured by SCL-90 (Bandini et al., 2011). Among self-identified transgender men, 60% reported to have experienced severe child abuse (Devor, 1994). A Hungarian study found that gender dysphoric

individuals who sought gender-affirming treatment had experienced more maternal dominance, emotional abuse, and neglect during childhood compared with controls. Assigned males at birth were also more exposed to disengaged mothers and more emotional neglect or criticism from their fathers (Simon et al., 2011). Finally, in a sample of transgender women and transgender men seeking evaluation prior to gender-affirming treatment, 77% reported being verbally abused, 58% were made to feel guilty by their parents, and 55% reported to be victims of childhood sexual abuse (Gehring & Knudson, 2005).

Whether childhood maltreatment, adult victimization, and/or sexual abuse were associated with psychiatric morbidity was addressed in Study IV.

Criminality

Criminality leading to prosecution was reported by 6/99 (6.1%) of transgender men and 13/134 (9.7%) of transgender women at the application of legal and surgical reassignment (Landén et al., 1998a) and incarceration was more common among combat veterans with a gender dysphoria diagnosis compared with those without such a diagnosis (Brown & Jones, 2015).

1.14 OUTCOME

The aim of gender-confirmation treatment is to ease gender dysphoria and for the individual to become as gender congruent (defined by the individual themselves) as possible. Thus the primary outcome measures are gender congruence, reduced gender dysphoria, global clinical impression improvement, quality of life, and not regretting the procedure.

Reduced psychiatric comorbidity and better psychological well-being are often used as secondary outcome measures. Moreover, it is important to monitor the safety and potential side effects of gender-affirming treatment.

A meta-analysis of outcome studies of post cross-sex hormone treatment up to 2005 concluded that approximately 80% experienced improvement in terms of gender dysphoria and quality of life (Murad et al., 2010). However, the quality of studies was low, with many lost to follow-up and a lack of control subjects. Later longitudinal studies and retrospective studies post gender-affirming treatment of participants diagnosed with any of the gender dysphoria diagnoses have confirmed the results, finding subjective improvement, less gender dysphoria, no or few regrets, and less psychopathological symptoms (Colizzi, et al.,, 2013; Colizzi, et al., 2014; De Cuypere et al., 2006; de Vries et al., 2014; Heylens et al., 2014b; Johansson, Sundbom, Höjerback, & Bodlund, 2010; Manieri et al., 2014; Pimenoff & Pfäfflin, 2011; Ruppin &

Pfafflin, 2015; Udeze, Abdelmawla, Khoosal, & Terry, 2008). It should be noted that four of the studies had a short follow-up time ranging from 3 to 12 months (Colizzi et al., 2013, 2014; Heylens et al., 2014b; Udenze et al., 2008). The studies with longer follow-up time (5-13 years) are on the other hand flawed by high dropout rates (16-49%), and relatively small samples (32-71 participants) (Johansson et al., 2010; Pimenhoff & Pfäfflin 2011; Rupper &Pfäfflin 2015; De Cuypere et al., 2006.). Table 6 presents an overview of Swedish follow-up studies.

Table 6. Swedish outcome studies of legal and medical transition.

Author	Study design	Time period	Parti-cipants	Response rate %	Follow-up time mean, (min-max) in years	Suicide /deceased of other reasons	Regret %	Patient evaluation improved or unchanged %	Clinician evaluation improved, unchanged or worsened %
Wålinder & Thuwe (1975)	P	1962-1974	24 (13 TW, 11 TM)	100	≥3	1	All 8 TW 15	NS	79
Lindemalm et al. (1986)	C-S	1979	13 TW	87	12 (6-25)	1	TW 31	NS	69
Bodlund et al. (1996)	P	NS	19 (10 TW, 9 TM)	100	5	0	All 5 TW 10	+ 63 +- 32	+ 68 - 16
Eldh et al. (1997)	C-S	1965-1995	90 (50 TW, 40 TW)	66	5.8 (0.5-30)	3 /3	All 4 TW 4 TM 5	+ 86	overall satisfied
Landén et al. (1998b)	R		205 (115 TW, 90 TM)	100	7.4 (NS)	N/A	All 4 TW 4 TM 3	N/A	N/A
Johansson et al. (2010)	P	NS	42 (25 TW, 17 TM)	70	9.0 (4-16)	0/1	0	+ 95	+ TW 72, TM 47 +- TW 20, TM 30

C-S = cross-sectional; N/A = not applicable; NS = not stated; P = prospective, R = retrospective; TM = Transgender men; TW = Transgender women; + = improved; +- = unchanged; - = worsened.

Regrets to the procedure

Regretting having undergone legal and medical transition is a dire outcome. Since the start of gender-affirming treatment, this has constantly been on the agenda: how to avoid regrets, and how to best identify risk factors for regret. Gender-affirming treatment is mostly performed in steps. This gives the individual time to evaluate each step before undergoing irreversible genital surgery. During this time, there are individuals who stop medical transition and reverse their gender role to their assigned sex at birth. It is not known how common these types of regrets are. In the literature, regret is either measured as legal regret applications or by explicitly asking persons if they regret the procedure or wish to re-transition. In early Swedish follow-up studies (3-12 years mean follow-up time), the regret rate was 8-31% (Lindemalm, Körlin, & Uddenberg, 1986; Lindemalm, Körlin, & Uddenberg, 1987; Wålinder & Thuwe, 1975).

Landén, Wålinder, Hambert, & Lundström (1998b) assessed legal regret applications to the National Board of Health and Welfare from 1973-1996 and found a regret rate of 3.8% (4.3% transgender women and 3.25% transgender men). In Germany and the Netherlands, regrets rates of 0.4-0.6% have been reported (Meyer zu Hoberge, 2009; van Kesteren, Asscheman, Megens, & Gooren, 1997; Weitze & Osburg, 1996).

Postoperative regrets were examined in Study II

Prognostic outcome factors

Various positive prognostic factors regarding outcomes after legal and medical transition have been suggested.

Good family support, and being in a relation (Bodlund & Kullgren, 1996; Landén et al., 1998b; Wålinder et al, 1978), good surgical result (De Cuypere et al., 2005; Eldh et al., 1997; Lawrence, 2003; Lundström et al., 1984; Pfäfflin, & Junge, 1992; Ross & Need, 1989), successful social transition, good diagnostics and proper care (Pfäfflin & Junge ,1992; Eldh et al., 1997) being read as and perceived by others in accordance with experienced gender identity (De Cuypere et al., 2006; Eldh et al., 1997; Ross & Need, 1989), being assigned female at birth (Smith, van Goozen, Kuiper, & Cohen-Kettenis, 2005; Blanchard, 1989; Pauly, 1981; Bodlund & Kullgren, 1996; Wålinder et al., 1978; Wålinder & Thuwe, 1975, Landén et al., 1998b), and positive self-image (Bodlund & Kullgren, 1996) have been identified with fewer regrets and/or positive outcomes of legal and medical transition. Some studies identified older age, secondary transsexualism, late onset or gynephilic transgender women as risk factors (Landén et al., 1998b; Blanchard et al., 1987; De Cuypere et al., 2006; Eldh et al., 1997; Lindemalm et al., 1987; Lothstein, 1979; Pfäfflin & Junge, 1992; Smith et al., 2005; Sørensen, 1981; Wålinder et al., 1978). Later studies have not confirmed any differences in outcome related to gender, sexual orientation or age of onset (Colizzi et al., 2013; Colizzi et al., 2015; Gorin-Lazard et al., 2013; Heylens, et al., 2014; Johansson et al., 2010; Ruppin & Pfäfflin, 2015).

Prior psychiatric morbidity, personality disorder, or social instability has also been seen as predictors for regrets or suboptimal outcomes (Bodlund & Kullgren, 1996; Landén et al., 1998b; Wålinder et al., 1978). However, Landén et al., (1998b) found that a history of psychotic disorders but not psychiatric treatment *per se* was a negative predictor. The co-occurrence of a psychotic disorder has been seen as a risk factor due to diagnostic difficulties, difficulties to assess expectations, and that the hormone treatment might impair the psychotic symptoms (Borras, Huguelet, & Eytan, 2007; Landén, 1999). Intrestingly, Meijer and coworkers (2017)

recently reported of four individuals with gender dysphoria and schizophrenia related diagnoses who received gender-affirming treatment. At follow-up at least three years since start of hormone treatment, satisfaction rate was high and stabilization of psychotic symptoms was seen (Meijer, Eeckhout, van Vlerken, & de Vries, 2017).

Interestingly one study compared patients who had been compliant to their treatment plan and found no differences in outcome (Pimenoff & Pfäfflin, 2011).Whether high sexual activity prior to treatment is negative as reported by Wålinder et al. (1978) or low sexual activity is negative as reported by Lindemalm et al. (1987) has not been evaluated in other studies.

2 AIMS OF THE THESIS

The overall aim of this thesis was to explore the neurobiological underpinnings of gender dysphoria, study secular trends in incidence, and study health and mortality following gender-affirming health care.

2.1 SPECIFIC AIMS

The specific aims and research questions were:

Study I

To examine whether gynephilic transgender women (assigned male at birth, female identified, attracted to women) differ from cisgender female and male controls regarding cerebral activation when exposed to odorous steroids prior to hormone treatment.

Study II

To describe the prevalence and incidence of applications for change of legal sex, genital surgery, and regret over the procedure during 1960-2010. Additional aims were to examine changes over time with respect to sex ratio, applicants' age, average time elapsed from first visit to being granted a new legal gender, reasons for application rejection, and number of individuals choosing surgical treatment abroad.

Study III

To analyze long-term mortality, psychiatric morbidity, and criminality after legal gender reassignment and gender-affirming genital surgery 1973-2003 in a nationwide cohort study.

Study IV

To study the outcomes of gender-affirming health care and legal gender transition in terms of gender congruence, global improvement, and psychiatric morbidity. Additional aims were to evaluate whether childhood adversities and adult stressful life events predicted psychiatric morbidity post transition.

3 METHODS

The studies included in this thesis used different designs, populations, data and statistical methods depending on the research question (Table 7).

Table 7. Summary of aims and methods applied in Study I-IV.

Study	Research question / study aim	Design /time period	Study population/ diagnostic manual/ stage of transition	Data
I	Do transgender women differ from cisgender controls regarding cerebral activation if exposed to steroid odorous compounds?	Experimental 2001-2006	12 gynephilic TW/ ICD-10/ pre gender-affirming treatment	PET images of cRBF
II	Incidence of applications for change of legal sex and permission for gender-affirming genital surgery, including postoperative regret	Descriptive 1960-2010	767 (289 TM, 478 TW)/ Wålinder, ICD8-10/ application for legal and genital surgical transition	Applications for legal and surgical reassignment
III	Long-term mortality, psychiatric morbidity, after legal reassignment and gender-affirming genital surgery	A population-based, matched case cohort study 1973-2010	324 (133 TM, 191 TW)/ ICD8-10/ post legal and surgical transition	Linked data from Swedish registers
IV	Outcome post transition regarding gender congruence, psychiatric morbidity, and its relation to adversities in childhood and adult life	Cross-sectional follow-up study 2006-2009	65 (16 men [AFAB], 49 women [AMAB])/ ICD8-10/ post legal and surgical transition	Self-constructed questionnaire, GCI-I, MINI, ASRS, AQ, AUDIT

AFAB = assigned female at birth; AMAB = assigned male at birth; ASRS = Adult Self-Report Scale Screener; AQ = The Autism Spectrum Quotient; AUDIT = Alcohol Use Disorders Identification Test; CGI-I = Clinical Global Impression Improvement; cRBF = cerebral regional blood flow; MINI = Mini International Neuropsychiatric Interview; PET = positron emission tomography; TM = transgender men; TW = transgender women.

3.1 STUDY I

In Study I, we investigated whether transgender women differed from cisgender female and male controls regarding cerebral activation when exposed to odorous steroids prior to hormone treatment. We performed functional neuroimaging and used positron emission tomography (PET) to characterize cerebral activation through regional cerebral blood flow (rCBF) patterns.

Participants and controls

Twelve gynephilic transgender women, diagnosed with Transsexualism (F64.0, ICD-10) during 2001-2006 were enrolled. The sampling procedure was opportunistic.

The diagnostic evaluation was made by transgender-experienced psychiatrists and psychologists at the Gender Team in Stockholm. Age at onset of gender dysphoria was prior

to 7 years for all except for one participant who reported debut at puberty. Sexual orientation was assessed with a modified Kinsey scale (0 = only heterosexual behavior to 6 = only homosexual behavior). It was explained to the participants that the scale was devised for cisgender persons and they were asked to rate themselves according with their gender assigned sex at birth. Nine participants scored between 0-2 on the Kinsey scale (Kinsey & Martin, 1948). Three participants had not yet had a sexual relationship, but all reported gynephilic sexual attraction and were thus classified as gynephilic.

All participants were unmedicated. No participants had received hormonal treatment with sex steroids, and blood analyses confirmed no current use of hormonal treatment.

The controls were 12 heterosexual, (scoring zero at the Kinsey scale) cisgender females and 12 heterosexual cisgender males. The cisgender male controls were somewhat younger than the other two groups but otherwise the groups were comparable with respect to age and education level (Table 8).

Table 8. Age and length of education of participants and controls.

	Transgender women	**Cisgender female controls**	**Cisgender male controls**
Mean (SD) age, years	32 (8)	33(6)	26 (2)
Mean (SD) length of education, years	12 (3)	13 (2)	13 (2)

Pet and MRI experiments

The experiments were carried out during the period 2001-2006 at Karolinska PET center by the same personnel, at the same time of day, with a standardized room temperature and air pressure. The procedure included structural magnetic resonance imaging (MRI) scans and functional PET images measuring rCBF with 15O H2O. The odorous compounds used for passive smelling during the activation condition consisted of 4,6-androstadien-3-one (AND), estra-1,3,5(10),16-tetraen-3-ol (EST), and four different common odors (OO), which consisted of lavender oil, cedar oil, eugenol, and butanol. During the PET experiment, all of the stimuli were presented in glass bottles at a distance of 10 mm from the nose. AND and EST were presented in crystalline and odorous form (200 mg, Steraloids, Newport, RI). Lavender oil, cedar oil, and eugenol were undiluted. The butanol solution had a concentration of 10%.

The activation condition consisted of passive smelling of AND, EST, and OO measured as alterations in rCBF patterns. Measurements were made at baseline (= smelling of odorless room air [AIR]) and during three stimulus conditions (= smelling AND, EST and OO). In total, there were twelve scans per person. After the scans the participants were presented with the odorants again and asked to rate the pleasantness, irritability, intensity, and familiarity using a 100 mm

visual analogue scale ranging from "very pleasant" to "very unpleasant", respectively. PET and MRI images were registered into a common space and spatially filtered in order to improve the signal in both structural and functional image content. Significant activations were determined using the Statistical Parametric Mapping software (SPM99, Wellcome Foundation, London, UK) (Frackowiak, 2004; Friston, Holmes, & Worsley, 1999; Friston, Holmes, Poline, Price, & Frith, 1996). In order to locate the areas of activation in the hypothalamus, we used the Schaltenbrant's Atlas (Schaltenbrand & Bailey, 1959) after translation of the Talairach's coordinates (Talairach & Tournoux, 1988).

Statistical analyses

We performed analyses at the whole-brain level and at the regional level of the hypothalamus, in order to define the spatial extent of how AND and EST activated the brain in each group, and to detect between-group differences and similarities. Broadly, three types of statistical analyses were performed in SPM99. The analyses pertained to within-group activations, between-group activations, and common activations across groups. Cluster-based statistics with correction for multiple comparisons at cluster level were used in the analyses, $p<0.05$ cluster correction.

3.2 STUDY II

In Study II, we examined applications for change of legal sex, and permission for genital surgery, as well as postoperative regret. All applications to the National Board of Health and Welfare from 1960-2010 were reviewed. Files from January 1, 2011 to June 30, 2011 were also analyzed in order to determine whether or not applications were approved.

Incidence was calculated and stratified for four periods between 1972 and 2010. The means of the total Swedish population over 17 years of age for the first and the last year of the 10-year intervals were used for incidence calculations (Sweden Statistics, 2012).

Prevalence was calculated based on all persons who ever applied for a new legal gender with the assumption that all were alive during the study period.

The regret rate was estimated by dividing the number of sex-reassigned individuals who later applied for reversal to their original sex with the total number of individuals who received a new legal gender. The data were stratified in 10-year time periods.

Statistical analyses

For descriptive statistics mean (SD) and median (min-max) were calculated. Dichotomous data were analyzed with Chi-2 or Fisher's exact test, as appropriate. Results were defined statistically significant if the p-value was < 0.0001.

All tables and statistical analyses were generated in the software package *R: A Language and Environment for statistical computing.* R Core Team.

3.3 STUDY III

In Study III, we explored long-term mortality and psychiatric morbidity following sex reassignment in a nation-wide cohort study (1973-2003). The study population and outcomes were identified by linking several Swedish national registers. Table 3.1.3.2 presents an overview of the registers used.

Participants

Definition and identification of cases

A person was defined as case exposed to legal and surgical gender reassignment if two criteria were met:

1. at least one inpatient admission with a gender dysphoria diagnosis without any concomitant psychiatric diagnosis in the Hospital Discharge Register, and
2. at least one discrepancy between the sex variable in the Medical Birth Register (from 1973 and onwards) or the National Censuses, and the latest sex designation in the Total Population Register

The first criterion was employed to capture hospitalization for sex reassignment surgery and served to secure the diagnosis and provide a time point for sex reassignment surgery. The second criterion was used to ensure that the person went through all steps in sex reassignment and eventually changed sex legally. Using these criteria, a total of 804 patients with Gender Identity Disorder were identified, of whom 324 displayed a shift in the sex variable during the period 1973-2003. The remaining 480 persons that did not shift gender variable comprised persons who either did not apply, or were not approved, for gender-affirming genital surgery. Moreover, the ICD-9 code 302 is a non-specific code for sexual disorders. Hence, this group might also comprise persons hospitalized for sexual disorders other than a gender dysphoria diagnosis. These 480 cases were therefore omitted from further analyses.

Start of follow-up

Start of follow-up was chosen as the estimated date of legal sex reassignment.

Definition and identification of population-based controls (unexposed group)

A person was defined as unexposed if there were no discrepancies in sex designation across the Censuses, Medical Birth, and Total Population registers and no gender identity disorder diagnosis was recorded in the Hospital Discharge Register. Two groups of 10 unexposed controls for each case were matched for birth year and for sex (one group for assigned sex at birth, and one group for reassigned sex). The controls had to be alive and residing in Sweden at the estimated sex reassignment date of the index person.

Measurements

The outcomes and covariates of interest were taken from Swedish registers. Table 9 describes the outcome measures, covariates, and corresponding registers. Each individual could contribute with several outcomes but only one event per outcome.

Statistical analyses

Each individual contributed person-time from study entry (for exposed: date of sex reassignment; for unexposed: date of sex reassignment of matched case) until date of outcome event, death, emigration, or end of study period (December 31, 2003), whichever came first.

The association between exposure (sex reassignment) and outcome (mortality, morbidity, crime) was measured by hazard ratios (HR) with 95% CI, taking follow-up time into account. HRs were estimated from proportional hazard regression models, stratified on matched sets (1:10) to account for the matching by sex, age, and calendar time (birth year). Crude HRs (though adjusted for sex and age through matching) and confounder-adjusted HRs (aHRs) were presented for all outcomes.

The two potential confounders, immigrant status (Yes/No) and history of severe psychiatric morbidity (Yes/No) prior to sex reassignment, were chosen based on previous research (Bodlund & Kullgren, 1996; Landén et al., 1998a). Gender-separated analyses were performed and a Kaplan-Meier survival plot graphically illustrates the survival of the sex-reassigned cohort and matched controls (all-cause mortality) over time. The significance level was set at p-value < 0.05 (all tests were two-sided). The data were analyzed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

Table 9. Outcome measures, definitions/ICD codes and corresponding registers.

Outcome measures		Register	Definitions/ICD codes
All causes of mortality		Cause of Death Register (CDR)	Registered as deceased
	Death by definite/uncertain suicide	Cause of Death Register (CDR)	ICD-8 codes and ICD-9 codes E950-E959 and E980-E989 ICD-10 codes X60-X84 and Y10-Y34
	Death by cardiovascular disease	Cause of Death Register (CDR)	ICD-8 codes 390-458 ICD-9 codes 390-459 ICD-10 codes I00-I99
	Death by tumor	Cause of Death Register (CDR)	ICD-8 codes and ICD-9 codes 140-239 ICD-10 codes C00-D48
Any inward care for			
	Any psychiatric disorder (gender dysphoria diagnosis excluded)	The Hospital Discharge Register (HDR)	ICD-8 codes 290-301 and 303-315 ICD-9 codes 290-301 and 303-319 ICD-10 codes F00-F63 and F65-F99
	Alcohol/substance abuse	The Hospital Discharge Register (HDR)	ICD-8 codes 303-304 ICD-9 codes 303-305, tobacco use disorder excluded ICD-10 codes F10-F16 and F18-F19, x5 excluded
	Definite /uncertain suicide attempt	The Hospital Discharge Register (HDR)	ICD-8 and ICD-9 codes E950-E959, E980-989 ICD-10 codes X60-X84, Y10-34
	Accidents	The Hospital Discharge Register (HDR)	ICD-8 and ICD-9 codes E800-E929 ICD-10 codes V01-X59
Convictions			
	Any criminal conviction	The Crime Register (CR)	Any criminal conviction in the CR
	Any violent conviction	The Crime Register (CR)	Any violent conviction was defined as homicide, aggravated assault and assaults, robbery, threatening behavior, harassment, arson or any sexual offence, in the CR
Covariates			
Severe psychiatric morbidity		The Hospital Discharge Register (HDR)	Any psychiatric morbidity excluding dementia and organic psychiatric symptoms, tobacco use, sleeping disorders, sexual dysfunctions, postpartum conditions, habit and impulse disorders. ICD-8 codes 291, 295-301, 303-304 and 307 ICD-9 codes 291-292, 295-298, 300-301, 303-305 (tobacco use disorder excluded), 307.1, 307.5, 308-309 and 311 ICD-10 codes F10-F16, F18-F25, F28-F45, F48, F50 and F60-F62.
Immigrant status		Total Population Register (TPR)	Defined as individuals born abroad

3.4 STUDY IV

In Study IV, we examined outcomes following medical and legal gender transition (mean (SD) follow-up time 7.2 (7.3) years) through individual interviews of 16 men (assigned female at birth) and 49 women (assigned male at birth).

Participants

Individuals in Sweden who had undergone gender-affirming health care and had changed their legal gender status at least 9 months prior to the examination were invited to participate

in this study during 2006-2010. A convenience sample was recruited via transgender organizations and transgender health care units in Sweden. Figure 1 outlines the study population.

Individuals in Sweden who had undergone gender-affirming health care and had changed their legal gender status at least 9 months prior to the examination were invited to participate in this study during 2006-2010. A convenience sample was recruited via transgender organizations and transgender health care units in Sweden. Figure 1 outlines the study population.

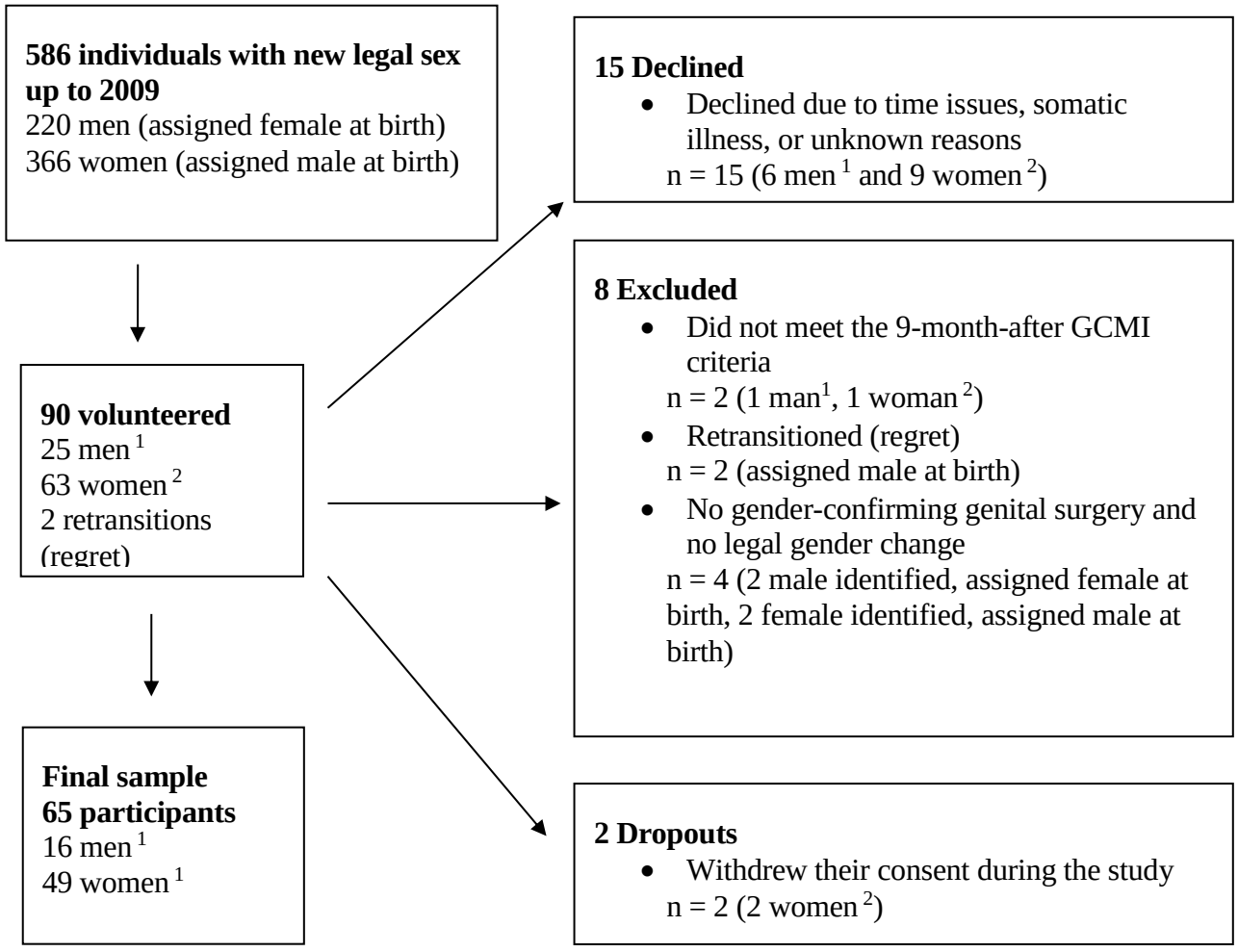

Figure 1. Flowchart of study population. [1] Men = individuals assigned female at birth but who identify as males and have been surgically and legally reassigned as men. [2] Women = individuals assigned male at birth but who identify as females and have been surgically and legally reassigned as women.

Measurements

Self-developed questionnaire

A questionnaire was developed to obtain sociodemographic information, history of treatment of gender dysphoria, questions about gender congruence, requests for re-transition, self-identification, how the subjects were perceived by others, subjects' satisfaction with their physical appearance with regards to aspects of femininity or masculinity, childhood adversities, and adult stressful life events. The questionnaire also recorded sexual orientation, age of onset of gender dysphoria, and history of suicide attempts.

Clinical Global Impression Improvement (CGI-I)

The participants rated their overall improvement after gender-affirming medical interventions and change of legal gender with the Clinical Global Impression Improvement Scale (CGI-I), graded from 0, ("very much worse") to 6 ("very much improved"). The CGI-I was dichotomized into either improved ("very much improved" or "very improved" [scoring 6 and 5]) or "not improved" (scoring < 5).

Mini International Neuropsychiatric Interview (M.I.N.I. 5.0.0b)

Psychiatric morbidity was assessed with the Mini International Neuropsychiatric Interview (MINI 5.0.0b), which is a structured interview for the assessment of current and lifetime psychiatric morbidity according to the DSM-IV (Sheehan et al., 1998). M.I.N.I. interviews were conducted by either a consultant psychiatrist or a trained research nurse.

Adult ADHD Self-Report Scale Screener (ASRS-V1.1 Screener)

The Adult ADHD Self-Report Scale Screener (ASRS-V1.1 Screener) was used to screen for attention-deficit/hyperactivity disorder (ADHD). The ASRS-V1.1 screener is the official WHO screening instrument for ADHD that correlates with the full ASRS version (Kessler et al., 2007). The screener has four inattention items and two hyperactivity items. The likelihood of a clinical diagnosis of ADHD is high if 4 of 6 criteria are met (Kessler et al., 2007).

The Autism Spectrum Quotient (AQ)

The Autism Spectrum Quotient (AQ) Scale was used to screen for autistic traits. The AQ was developed to provide a brief self-report measure of autistic traits (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001). The maximum score is 50. A cut-off score of 32 has been shown to be an acceptable sensitivity (0.77) and specificity (0.74) for capturing an autism spectrum diagnosis (Woodbury-Smith, Robinson, Wheelwright, & Baron-Cohen, 2005).

Alcohol Use Disorders Identification Test (AUDIT)

Alcohol use was measured by the Swedish version of the Alcohol Use Disorders Identification Test (AUDIT), which has been validated to identify hazardous patterns of alcohol consumption (Bergman & Källmén, 2002; Bohn, Babor, & Kranzler, 1995). The scale comprises 10 items and the maximum total score is 40 points. Scores above 6 for cisgender women and above 8 for cisgender men are regarded as indicators of harmful drinking (Berman, Wennberg, & Källmén, 2012).

Questions about sexual abuse

The questions about sexual abuse have been used previously in a national population-based study in Sweden, "Sex in Sweden" (Swedish National Institute of Public Health, 2000), which enabled us to compare results of this study with population data.

Statistical analyses

Descriptive data were expressed as means (SD) and medians (range) for continuous variables, and as numbers (percentages) for categorical variables. Percentages were calculated based on those who completed the respective questions. For group comparison, the Mann-Whitney U test for group comparisons of continuous or ordinal variables was used since the data did not meet the assumptions of a normal distribution according to the Kolmogorov-Smirnov test. For categorical variables, Fisher's exact test and chi-square were used as appropriate. A logistic regression analysis was performed to test which variables were associated with a current psychiatric illness. The dependent variable was current psychiatric morbidity (Yes/No). Predictor variables with $p < 0.05$ (Table 5) were considered for inclusion in the model. These variables were: childhood maltreatment, childhood sexual abuse, born abroad, not accepted in assigned gender, and victim of a crime related to transgender background. Given the low number of study subjects, the number of predictor variables in a logistic regression analysis should preferably be 4 or less. We therefore merged childhood maltreatment and childhood sexual abuse into one predictor variable. Being on sick leave and not being accepted in the assigned gender at work was considered to be a consequence of having a psychiatric disorder and therefore was not included in the model. A forward stepwise elimination via the Wald statistics ("Enter") was used. A p-value < 0.05 was regarded as significant. The statistic calculations were done using *IBM SPSS Statistics 22*. SPSS, Chicago, IL, USA.

3.5 ETHICAL CONSIDERATIONS

All studies were approved by the Regional Ethical Review Board in Stockholm. The National Board of Health and Welfare granted permission to review the files of all applications for legal and surgical gender reassignment.

In Study I and IV all participants and controls gave informed consent to participate and the studies were conducted according to the Helsinki declaration.

4 MAIN RESULTS

4.1 STUDY I, NEUROBIOLOGICAL TRAITS

In the whole-brain analysis, cisgender females and males differed in their brain activation when smelling the steroidal compounds, AND and EST. In cisgender females, anterior hypothalamus was activated when smelling AND and olfactory parts of the brain when smelling EST. In cisgender males, the posterior hypothalamus was activated when smelling EST and olfactory parts of the brain when smelling AND. There were no differences when participants smelled common odors.

Transgender women differed significantly from cisgender males, but not cisgender women, in how the brain was activated when smelling AND and EST. There were no differences in brain activation from cisgender controls when they smelled common odors.

To examine not only if they differed from cisgender controls but also shared activation clusters, conjunctional analyses were made. The result of the conjunctional analyses showed that not only AND but also EST elicited a hypothalamic brain activation. Thus they shared hypothalamic activation for AND with cisgender women and for EST with cisgender men. However, the hypothalamic activation caused by EST was less strong than that caused by AND. Hence, despite a common cluster seen in the conjunctional analyses with cisgender males, they did not differ significantly when compared directly with cisgender female controls regarding the EST activation. The regional post-hoc analyses, in predefined areas of the hypothalamus, did not reveal anything further.

In conclusion, transgender women activated the brain in response to the steroidal compound AND in the same way as cisgender women, and differently to cisgender males. However, they also had cisgender male features when smelling EST, albeit not strong enough to make them different from cisgender women.

Strength and limitations

Not only perceived gender identity seems to effect hypothalamic response to AND and EST, but also sexual orientation. Homosexual (androphilic) cisgender males had a similar hypothalamus activation pattern to cisgender women (Savic et al., 2005). In this study, the transgender women were gynephilic and thus homosexual in relation to their gender identity. Whether the hypothalamic response to AND and EST is driven by perceived gender identity, and or sexual orientation towards someone with the same gender identity needs to be further examined. All but one of the transgender participants stated that they had gender dysphoric feeling before the age of 7 years old, but we did not assess whether they fulfilled the diagnostic

criteria for gender dysphoria in childhood. A strength is that the diagnostic assessment was performed by an experienced gender team and that all transgender participants were diagnosed with Transsexualism F64.0 (World Health Organization, 1992).

4.2 STUDY II, INCIDENCE OF GENDER DYSPHORIA AND POSTOPERATIV REGRETS

Number of applications, age, sex ratio, and outcome

A total of 767 people (289 assigned female at birth and 478 assigned male at birth) applied for legal and surgical sex reassignment in Sweden due to gender dysphoria during the period 1960-2010 (Figure 2). Of these 767 applicants, 89% or 681 persons (transgender men: 252/289, 87%; transgender women 429/478, 90%) were granted a new legal gender and had undergone gender-affirmation surgery by the end of June, 2011. The median (min-max) age at application for the whole period was 27 years (16-65) for transgender men and 32 years (15-75) for transgender women.

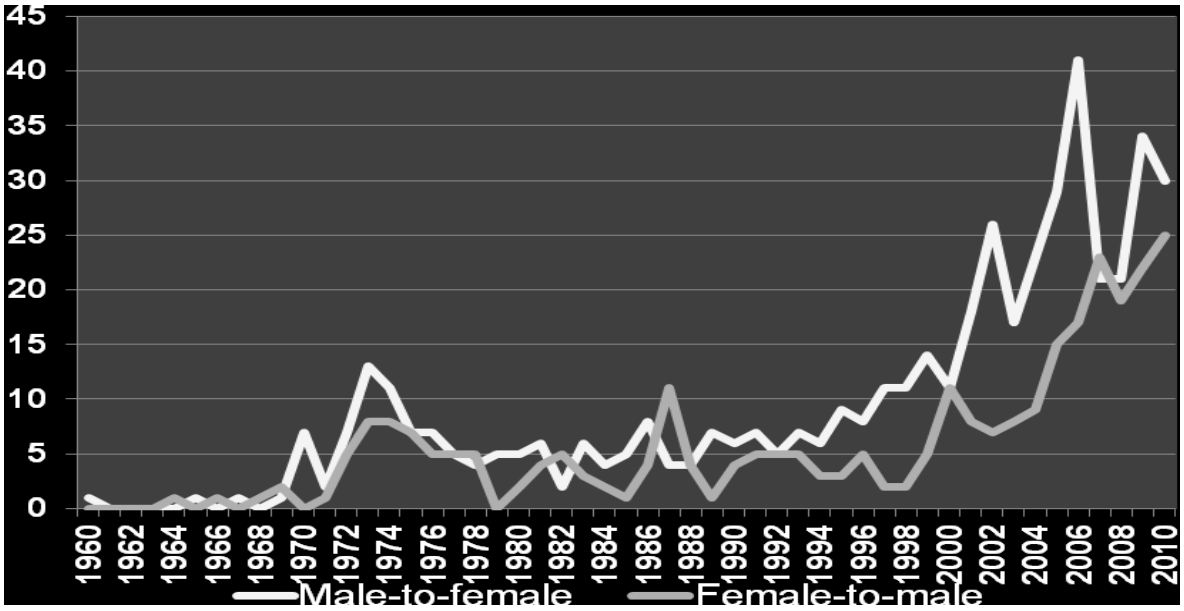

Figure 2. New applicants for a new legal sex and permission for gender-affirming genital surgery to the National Board of Health and Welfare in Sweden 1960-2010, per year, males and females as assigned at birth.

Incidence

The incidence of applications was calculated and stratified over four periods between 1972 and 2010. For transgender men, the incidence increased from 0.16 to 0.42/100,000/year. For transgender women, the incidence increased from 0.23 to 0.73/100,000/year. The most dramatic increase occurred during the period 2001-2010.

The proportion of transgender men 30 years or older at the time of application remained stable at around 30%. In contrast, the proportion of transgender women 30 years or older increased from 37% in the first decade to 60% in the latter three decades.

For the whole period (1960-2010), the transgender men: transgender women ratio was 1:1.66, but fluctuated over time: 1:1.42 (1972-1980), 1:1.33 (1981-1990), 1:1.93 (1991-2000) and 1:1.70 (2001-2010).

Prevalence

The point prevalence at December 31, 2010 for persons who applied for a new legal gender was for transgender men 1:13,120 (0.008%) and for transgender women 1:7,750 (0.013%).

Postoperative regrets

A total of 15 individuals (5 transgender men and 10 transgender women) out of 681 who received a new legal gender between 1960-2010 applied for reversal to the gender assigned at birth (regret applications). This corresponds to a regret rate of 2.2% for both sexes (2.0% transgender men and 2.3% transgender women). As showed in Table 11, the regret rate decreased significantly over the whole study period ($p < 0.0001$, Fisher's exact test). The median (min-max) age at which this group first applied for a new legal sex was 22 (18-52) years in transgender men and 35 (27-49) years in transgender women. The median (range) time elapsed from attaining a new legal gender to the regret application was 7.5 years (90 months, range 75-137) for transgender men, and 8.5 years (102 months, range 22-177) for transgender women.

Table 11. Individuals who subsequently apply for reversal to the original sex

Time period	Number of sex-reassigned individuals in the time period when they made their first application who later applied for reversal to the assigned sex at birth/ total number of individuals who made their first application in this time period and received a new legal sex (%)	Number of regret applications during that time period
1960-1971	4/15 (27)	0
1972-1980	6/103 (5.8)	5
1981-1990	1/76 (1.3)	3
1991-2000	3/127 (2.4)	3
2001-2010	1/360 (0.3)	4
1960-2010	15/681 (2.2)	15

Strengths and limitations

A limitation of Study II is that the point prevalence is slightly overestimated since we were not able to exclude those who died after sex reassignment and those who were born outside Sweden. We did not include data on sociodemographic variables, prior psychiatric morbidity, sexual orientation and onset age of gender dysphoria. Hence, we could not evaluate these factors in relation to the increased incidence, changes of sex ratio, and postoperative regret. Notably, the study examined applications for legal and surgical sex reassignment and not gender dysphoria diagnoses. However, a gender dysphoria diagnosis is required to be granted a new legal sex. This study is unique as it represents a complete national cohort of people who have applied for legal gender change in Sweden over the past 50 years. The quality of the data is assured by access to all the original files and applications since 1960 and by the legal framework regulating legal sex change in Sweden. The methodology was similar to previous Swedish studies, which allows for comparisons (Landén et al., 1996; Olsson & Möller, 2006; Wålinder, 1971).

4.3 OVERVIEW OF POSTTRANSITION OUTCOMES (STUDY III AND IV)

Table 12 shows an overview of outcomes in Study III and IV.

Table 12. Overview of study characteristics, sociodemographics and outcomes for participants in study III, IV.

Study	**Study III**	**Study IV**
Study characteristics		
Type of study	matched case control	cross-sectional
Time period	1973-2003	1972-2009
Number of participants	324	65
Follow-up time mean (SD, min-max)	11.4	7.2 (7.3, 0.75-30.5)
Age at legal and surgical reassignment mean (SD, min -max)	35.1 (9.7, 20-69)	36.2 (11.6, 18.1-64.6)
Sociodemographics n/N (%)		
Immigrant status, not born in Sweden	70/234 (22)[1]	10/63 (16) [2]
Urban living area	291/234 (10)[1]	53/63 (84)[2]
More than 10 years of schooling or post-high school prior to entry (Study III) or at examination (Study IV)	151/324 (58)[1]	39/64 (61)[2]
Outcome post transition n/N (%)		
Psychiatric inpatient care post transition (Study III) or current psychiatric morbidity assessed by MINI (Study IV)	64/324 (19.8)	16/65 (24.6)
Psychiatric inpatient care for suicide attempts post transition (Study III) or self-reported suicide attempt post transition (Study IV)	29/324 (9.0)	8/64 (12.5)
Alcohol/substance abuse inpatient care post transition or current hazardous drinking, assessed by AUDIT	22/324 (6.8)	1/65 (1.5)

[1] prior to study entry [2] at examination

4.4 STUDY III, MORTALITY, PSYCHIATRIC MORBIDITY POST TRANSITION

Characteristics of participants and controls prior to sex reassignment

Individuals who were post-legal and surgical transition were hospitalized for psychiatric morbidity other than Gender Identity Disorder prior to treatment about four times more often than cisgender controls. They were twice as likely to have immigrant status compared with cisgender controls. There were no significant differences between assigned females at birth or assigned males at birth regarding measured baseline characteristics.

Mortality

Individuals of both genders who had undergone legal and medical transition had approximately three times higher all-cause mortality than controls of sex assigned at birth, even after adjustment for covariates. Table 13 displays the various outcomes for the whole period, separated depending on whether the sex reassignment was performed 1973-1988 or 1989-2003. For the latter period the participants did not differ from controls. The higher all-cause mortality was also true when comparing with controls of reassigned sex and for both assigned females and male at birth analyzed separately. Kaplan-Meier curves show that survival of transgender men and transgender women start to diverge after about 10 years of follow-up.

Psychiatric morbidity and suicide attempts

Individuals of both genders who had undergone sex reassignment had an approximately three times higher risk of inpatient care for any psychiatric disorder other than gender dysphoria when adjusted for immigrant status and psychiatric morbidity prior to entry, compared with birth sex controls. This increase was seen regardless of whether the sex reassignment took place before or after 1989. In line with the increased mortality in suicide there was an increased risk of hospitalization for attempted suicide compared to controls for the period prior to 1989. There were no differences compared with controls regarding hospitalization for substance misuse or accidents.

Strengths and limitations

First, this study reflects the outcome of psychiatric and somatic treatment for gender dysphoria provided in Sweden during the 1970s and 1980s. Since then, treatment has evolved with improved gender-affirming surgery (Eldh et al., 1997; Sigurjonsson, Rinder, Möllermark, Farnebo, & Lundgren, 2015), refined hormonal treatment and more attention to psychosocial care (Hembree et al., 2009), which might have improved the outcome. Supporting this notion, the trans persons did not differ regarding mortality and suicide attempts compared with controls

during the last fifteen years of the follow-up period. On the other hand, the mortality rates started to diverge after 10 years and the mortality rate might increase for those included the last five years. Second, gender dysphoria is a rare condition and Sweden has a small population (9.2 million inhabitants in 2008). Hence, despite being based on a comparatively large national cohort and long-term follow-up, the statistical power was limited. Third, regarding psychiatric morbidity after sex reassignment, we assessed inpatient psychiatric care. Since most psychiatric care is provided in outpatient settings (for which no reliable data were available), underestimation of the *absolute* prevalence of psychiatric morbidity was inevitable. However, there is no reason to believe that this would change the *relative risks* for psychiatric morbidity unless individuals who are post legal and surgical transition were more likely than matched controls to be admitted to hospital for any given psychiatric condition. In other words, since the same approach was taken for cases and controls, this would not affect risk estimates if the same degree of underestimation occurred.

The strengths of this study include nationwide data collected representatively over more than 30 years, extensive follow-up time, absence of selection bias, and minimal loss to follow-up. Many previous studies suffer from low outcome ascertainment (De Cuypere et al., 2005; Eldh et al., 1997; Lawrence, 2003), but our study should have captured almost the entire population of sex-reassigned transgender individuals in Sweden during 1973-2003. Moreover, previous outcome studies have mixed pre-operative and post-operative transgender persons (Bodlund & Kullgren, 1996; Johansson et al., 2010; Vujovic et al., 2008), whereas we included only post-operative transgender persons evaluated clinically by a specialized psychiatrist or gender dysphoria team during at least 2 years and then re-evaluated by specialists at the National Board of Health and Welfare before becoming eligible for gender-affirming genital surgery and legal sex reassignment. Finally, whereas previous studies either lack a control group or use standardized mortality rates or standardized incidence rates as comparison (De Cuypere et al., 2005; Gooren, Giltay, & Bunck, 2008; van Kesteren et al., 1997), we selected random population controls matched by birth year, and either birth or final sex.

Table13. Risk of various outcomes among sex-reassigned subjects in Sweden (N=324) compared with population controls matched for birth year and birth sex.

Outcomes	Number of events cases/ controls 1973-2003	Outcome incidence rate per 1000 person-years 1973-2003 (95% CI)		Crude hazard ratio (95% CI) 1973-2003	Adjusted[1] hazard ratio (95% CI) 1973-2003	Adjusted[1] hazard ratio (95% CI) 1973-1988	Adjusted[1] hazard ratio (95% CI) 1989-2003
		Cases	Controls				
Any death	27/99	7.3 (5.0-10.6)	2.5 (2.0-3.0)	2.9 (1.9-4.5)	2.8 (1.8-4.3)	3.1 (1.9-5.0)	1.9 (0.7-5.0)
by suicide	10/5	2.7 (1.5-5.0)	0.1 (0.1-0.3)	19.1 (6.5-55.9)	19.1 (5.8-62.9)	N/A	N/A
by cardiovascular disease	9/42	2.4 (1.3-4.7)	1.1 (0.8-1.4)	2.6 (1.2-5.4)	2.5 (1.2-5.3)	N/A	N/A
by neoplasm	8/38	2.2 (1.1-4.3)	1.0 (0.7-1.3)	2.1 (1.0-4.6)	2.1 (1.0-4.6)	N/A	N/A
Any psychiatric hospitalization[2]	64/173	19.0 (14.8-24.2)	4.2 (3.6-4.9)	4.2 (3.1-5.6)	2.8 (2.0-3.9)	3.0 (1.9-4.6)	2.5 (1.4-4.2)
Substance abuse	22/78	5.9 (3.9-8.9)	1.8 (1.5-2.3)	3.0 (1.9-4.9)	1.7 (1.0-3.1)	N/A	N/A
Suicide attempt	29/44	7.9 (5.5-11.4)	1.0 (0.8-1.4)	7.6 (4.7-12.4)	4.9 (2.9-8.5)	7.9 (4.1-15.3)	2.0 (0.7-5.3)
Any accident	32/233	9.0 (6.3-12.7)	5.7 (5.0-6.5)	1.6 (1.1-2.3)	1.4 (1.0-2.1)	1.6 (1.0-2.5)	1.1 (0.5-2.2)
Any crime	60/350	18.5 (14.3-23.8)	9.0 (8.1-10.0)	1.9 (1.4-2.5)	1.3 (1.0-1.8)	1.6 (1.1-2.4)	0.9 (0.6-1.5)
Violent crime	14/61	3.6 (2.1-6.1)	1.4 (1.1-1.8)	2.7 (1.5-4.9)	1.5 (0.8-3.0)	N/A	N/A

[1] Adjusted for psychiatric morbidity prior to baseline and immigrant status.

[2] Hospitalizations for Gender Identity Disorder were excluded.

N/A = Not applicable due to sparse data

4.5 STUDY IV, GENDER CONGRUENCE, PSYCHIATRIC MORBIDITY, AND REALTION TO CHILDHOOD ADVERSITIES AND ADULT STRESSFUL LIFE EVENTS POST TRANSITION

Characteristics and sociodemographics of the participants

Sixty-five individuals (16 men assigned female at birth, and 49 women assigned male at birth) participated, which constitutes 11.1% (7.3% of men and 13.4% of women) of the total sex-reassigned population in Sweden at the time of the study. The mean (SD) follow-up time was 7.2 (7.3) years with a median of 4.3 (range 0.75-30.5) years.

Gender congruence, global clinical impression improvement

Gender congruence

The vast majority, 91.9% (57/62), felt gender-congruent after transition (men, 16/16, 100%; women, 41/46, 89.1%). Self-identification was in agreement with the new assigned gender for a majority (all, 49/61, 80.3%; men, 13/16, 81.3%; women, 36/45, 80.0%); the remaining individuals reported a transgender identity. More men (15/16, 93.8%) than women (34/46, 73.9%) reported that other people perceived them as being of their new assigned gender. All men and 37 of 46 (80.4%) women were satisfied with how their physical appearance reflected their assigned gender. No one expressed a wich to retransition.

Clinical Global Impression Improvement

With respect to improvement after gender-affirming health care as measured by CGI-I, a majority reported improvement (all, 52/64, 81.3%; men, 15/16, 93.8%; women, 37/48, 80.4%).

Suicide attempts and psychiatric morbidity

Lifetime suicide attempt was reported by 40%. All suicide attempts post transition were committed by women. There was a decrease in individuals reporting suicide attempts: 36% before versus 13% after. In the total cohort, 41.5% had any current or lifetime psychiatric diagnosis, and a quarter of the participants had one or more current psychiatric diagnoses. Depression was the most common diagnosis. No participant suffered from any present or previous psychosis. No participant met the criteria for current alcohol misuse or substance abuse disorder, but the AUDIT instrument revealed that 12.7% had hazardous alcohol consumption when the cut-off score for women was used and 4.8% when the cut-off score for men was used. According to the ASRS-V1.1 Screener, 13.3% of the participants screened positive for ADHD. One woman scored 32 on the AQ scale, indicating autism spectrum disorder.

Child adversities and adult stressful life events

More than 90% of the individuals had experienced some childhood adversity or some adult stressful life event. Any childhood adversity was reported by more than three quarters of the participants. All cases of childhood sexual abuse were reported by women.

At least one adult stressful life event was reported by more than three quarters of the participants. Harassments, discrimination, and being a victim of crimes related to their transgender background occurred both before, during, and after transition. Not being accepted

as the correct gender by at least one family member, health care worker, work or school colleague, or friend was reported by 56%. Almost one third reported sexual abuse as adults. The sexual abuse reported by the three men had occurred before transition. The 16 women who reported sexual abuse as adults were abused before, during, and after transition.

Relationship between psychiatric morbidity and childhood adversities

A quarter of the participants displayed some current psychiatric morbidity. A logistic regression analysis was performed to test which variables were associated with current psychiatric morbidity. Current psychiatric morbidity as predicted by being born abroad, childhood maltreatment or childhood sexual abuse, and not being accepted in assigned gender by at least one other party (Table 14).

Table14. Logistic regression analysis of current psychiatric morbidity (dependent variable) for selected clinical variables (see text).

	OR (95% CI)		p-value
Childhood maltreatment or sexual abuse	12.3	(2.0-77.9)	0.008
Not born in Sweden	18.3	(1.9-176.3)	0.012
Not accepted as correct gender by at least one family member, health care worker, work or school colleague, or friend	9.0	(1.5-52.2)	0.015
Victim of crime related to transgender background	2.3	(0.5-11.6)	0.292

Strengths and limitations

Low power due to small sample sizes is common in transgender research. We captured 11% of the total population that had changed their legal gender and underwent gender-affirming genital surgery in Sweden. In spite of this, our sample size was 65, which limits the statistical power. Further, the selection procedure was not random and a selection bias may have occurred. However, age at time for legal and social transition, immigrant status, living in cities, the high prevalence of psychiatric morbidity and suicide attempts is in line with previous register studies in Sweden that captured almost all sex-reassigned individuals (Dhejne et al., 2011). Also, the age of the study group matches the age of the group that we did not capture. Information on childhood adversities and adult stressful life events was sometimes captured long after the events occurred and might be subject to recall bias.

A strength of the study is that all participants were post transition and had no incentive to adjust their answers to achieve a desired treatment, which is common in studies prior to

gender-affirming health care. Indeed, one study reported that 44% of the participants gave a falsified story at assessment (Pimenoff & Pfäfflin, 2011).

5 GENERAL DISCUSSION

5.1 NEURAL CORRELATES OF GENDER DYSPHORIA

The results showed that gynephilic transgender women resembled cisgender female controls with regards to hypothalamic activation of steroids compounds AND and EST, even if they also shared activation patterns with cisgender males. The findings are in line with a recent functional magnetic resonance imaging (fMRI) study, which reported that gender dysphoric transgender adolescent girls and boys who smelled androstendione both had a hypothalamic activation pattern in line with their experienced gender identity (Burke, Cohen-Kettenis, Veltman, Klink, & Bakker, 2014). In contrast, prepubertal gender dysphoric boys had an activation pattern similar to cisgender boys, and prepubertal gender dysphoric girls were similar to neither cisgender girls nor to cisgender boys. Gender dysphoric prepubertal children are more heterogenic compared with gender dysphoric adolescents, which may explain the divergent results. Interestingly, the cisgender prepubertal and adolescent controls both showed gender differences in response to androstendione, thus indicating that the sex differences are present before puberty and maybe even be established prenatally (Burke et al., 2014). The findings that transgender women also shared some activation pattern with cisgender male controls accords with morphological and functional brain studies reporting that transgender individuals possess an intermediate position between cisgender females and males, or not resembling either of them (Junger et al., 2014; Junger et al., 2013; Kranz et al., 2014; Lin et al., 2014; Rametti, et al., 201a; Rametti et al., 2011a). Another line of neurobiological studies has instead of searching for resemblance or non-resemblance with cisgender females or males, investigated the experience per se of gender incongruence/gender dysphoria. They suggest that cerebral networks involved in body image and self-perception (the internal representation of physical appearance) could be altered in gender dysphoric individuals (Feusner, et al., 2016; Feusner, et al., 2016; Manzouri, Kosidou, & Savic, 2015). Questions have also been raised as to whether gender dysphoria is caused by the same mechanisms in transgender men, transgender women and other subgroups in the population (Smith et al., 2015). It has also been suggested that a spectrum view would be preferable to trying to fit in gender dysphoric individuals in more – or less – male or female features (Smith et al., 2015). Future studies should – besides ICD or DSM diagnoses – provide more detailed phenotypes and describe their participants on many different levels.

This study adds to the literature in that it indicates a neurobiological background to gender dysphoria. However, this notion does not have far-reaching clinical implications, as a brain scan cannot be used to find out whether or not a patient is suffering from gender dysphoria.

The diagnosis of gender dysphoria is currently based solely on medical history: the personal experience of gender incongruence, body dysphoria et cetera and whether any other condition better explains the feeling of gender incongruence or gender dysphoria (Bockting, Knudson, & Goldberg, 2006; Coleman et al., 2012).

5.2 INCREASE OF GENDER DYSPHORIA

We found that the incidence of application for legal and surgical sex reassignment increased dramatically over the 50-year study period. This parallels other reports and a recent meta-analysis (Arcelus et al., 2015). It has not yet been clarified why this increase has occurred. Among conceivable reasons are that more individuals come forward and seek help, and that more transgender persons are deemed eligible for sex reassignment. Gender dysphoria per se may also have increased in the population. Population studies of gender dysphoria are scarce, but suggest that what we see clinically is the tip of an iceberg. Gender dysphoric symptoms (feelings of gender incongruence and a wish for gender-affirming treatment) were in the Netherlands reported by 0.2% of assigned females and 0.6% of assigned males (Kuyper & Wijsen, 2013). Increased openness and visibility of transgender persons in the society and better access to care have been suggested as reasons prompting help-seeking behavior (Arcelus et al., 2015; Dhejne et al., 2014). Individuals with autism spectrum disorder or unstable psychosocial situations used to be seen as less eligible for legal and medical transition (Landén & Rasmussen, 1997; Lundström & Wålinder, 1985). This has slowly changed over the last twenty years, and could explain some of the increased incidence (Glidden et al., 2016).

Implications

Transgender health care in Sweden is not currently scaled for the increase in individuals seeking gender-affirming treatment. Hence, there are long waiting lists both to start evaluation, and to commence gender-affirming treatment. There is also a waiting list at the Board of National Health and Welfare that handles applications for a new legal gender and permission for gender-affirming genital surgery. Given that gender-affirming treatment and legal recognition decrease gender dysphoria (Heylens, et al., 2014b; Johansson et al., 2010; Murad et al., 2010), improve general health (Zeluf et al., 2016), and reduce psychiatric morbidity it is important to increase access to health care and legal gender recognition (Reisner et al., 2016b; Winter et al., 2016). With increasing numbers of transgender persons seeking health care, there is also a need for more general knowledge of transgender medicine in the whole health care system. Transgender medicine needs to be included in the education curriculum of all health care professionals (Arcelus & Bouman, 2015; Safer, 2016; Safer & Pearce, 2013).

5.3 MORTALITY

We found that individuals of both genders who had undergone legal and surgical transition 1973-2003 had an approximately three times higher all-cause mortality than controls of sex assigned at birth, even after adjustment for covariates. There was an improvement over time, and for the period 1989-2003 the participants did not differ from controls. Major causes of death were suicide and cardiovascular disease. Transgender persons did not differ from controls with regards to cancer. The findings accord with previous studies (Asscheman et al., 2011; Blosnich et al., 2014; Simonsen et al., 2016a), even though the Dutch study did not find any increased mortality for transgender men (Asscheman et al., 2011). The inconclusive finding regarding transgender men needs to be further examined. A recent review concludes that current data support the safety of physician-supervised cross-sex hormone treatment (Weinand & Safer, 2015), but long-term large studies regarding the safety aspects of transgender medicine are needed (Feldman et al., 2016; Reisner et al., 2016a; Weinand & Safer, 2015).

5.4 REGRETS

We found the regret rate to be 2.2% and declining. The regret rate is lower that reported by Landén et al. (1998b) (3.8%). However, Landén et al. (1998b) reported a mean latency for applying for reversal of 7.4 years, which matches the median latency time in our study: 7.5 years for assigned females at birth and 8.5 years for assigned males at birth. This means that some of the 360 individuals who were granted a new legal sex during 2001-2010 may later apply for retransition. Landén et al. (1998b) had the same disclaimer. Indeed, three additional individuals who received a new legal sex 1991-2000 regretted their transition.

However, the trend is fewer regret applications over time: 11 of the 15 regrets applied for a new legal gender before 1991. This could indicate that transgender health care – including the evaluation process, hormone treatment, and surgical treatment – has improved.

The rate of regret did not differ depending on assigned sex at birth, but the individuals who regretted the transition were somewhat older at the time of application than those who did not regret the procedure (median 35 years compared with 32), which is sometimes seen as a sign of late onset gender dysphoria. On the other hand, the proportion of applicants over 30 years old has been stable (60%) since 1981 and the regret rate is nevertheless declining. Recent follow-up studies have not found any difference in outcome in relation to gender, age of onset or sexual orientation (Johansson et al., 2010; Nieder et al., 2016). Predictors for regret in the study by Landén et al. (1998b) were poor family support, late onset gender dysphoria (secondary transsexualism) in trans women, and a history of psychotic disorders. Since then,

support to next-of-kin is included in Swedish transgender health care. This may have contributed to the declining regret rate and is in line with other studies reporting a better general outcome for those with good social support.

Studies that examined predictors for regret are hampered by small samples (Eldh et al., 1997; Landén et al., 1998b; Lindemalm et al., 1987) due to the low regret rate and low prevalence of gender dysphoria in the population. This may explain some discrepancies in the literature, such as whether or not late onset or secondary gender dysphoria are risk factors (Bodlund & Kullgren, 1996; Johansson et al., 2010; Landén et al., 1998b). Fear of regret probably underlies the recommended step-wise procedure including a diagnostic evaluation time, then initiation of reversible or partly reversible gender-affirming treatment prior to irreversible genital surgery (Coleman et al., 2012).The importance of a slow process is also mirrored in the Swedish legislation and in the Swedish national guidelines. However, we noted that the mean time between the first visit at any clinic for gender dysphoria and a new legal gender declined gradually from 7.25 years between 1972 and 1980, to 3.8 years between 2001 and 2010. At the same time the regret rate decreased from 5.8% to 0.3% indicating that a somewhat quicker process did not increase the regret rate. There is no study evaluating the association between regret and the evaluation time, but one study compared an early surgery group with a group of patients on a surgery waiting list and found better mental well-being in the operated group (Mate-Kole, Freschi, & Robin, 1990).

Implications

It is important to continue recording regrets. To go beyond quantitative studies and add qualitative studies would further our understanding of regret. Questions of interest would be: was the person actually gender dysphoric and received the correct treatment? Or was the person disappointed by the limits of gender-affirming treatments? Did the person regret certain steps, but not all of the gender-affirming treatment? Or did the person have other reasons to retransition? Randomized studies aiming to evaluate different evaluation and treatment protocols in relation to regret or less favorable outcomes would also be helpful

5.5 PSYCHIATRIC MORBIDITY, SUICIDALITY AND VULNERABILITY

We found that psychiatric morbidity, including suicide attempts, was more common in transgender persons compared with assumed cisgender controls. In the cross-sectional study, a quarter had a current psychiatric morbidity; depression and anxiety disorder were most common. Both findings accord with a recent review of mental health problems in the transgender group (Dhejne et al., 2016). The studies included in this thesis did not detect any

gender differences in contrast to older Swedish studies (Bodlund & Kullgren, 1996; Wålinder et al., 1978), but in line with other more recent studies (Claes et al., 2015; Duisin et al., 2014; Johansson et al., 2010). We were also unable to confirm the suboptimal outcomes in gynephilic transgender women compared to androphilic transgender women, as found in previous studies (Landén et al., 1998b; Smith et al., 2005). Gynephilic transgender women identify themselves as lesbians, and belonging to two minority groups may double the level of minority status stress. In recent years, being homosexual in Sweden has become less stigmatized (ILGA-Europe, 2013), which may have affected gynephilic transgender women positively. Transgender individuals have also been accepted as members in the Swedish LGBT community since 2001. This may have increased perceived social support which is correlated to mental wellbeing (Davey et al., 2014). In line with the decreasing regret rate, there was a positive trend over time where mortality rate and inpatient care for suicide attempts in transgender persons after gender transition did not differ from controls after 1989, even though the inpatient psychiatric care remained elevated. The positive time trend may reflect improved transgender health care in Sweden. More than 90% of the individuals (with no gender differences) in the cross-sectional study had experienced some childhood adversity or some adult stressful life event. Harassment, discrimination, and being a victim of crime related to their transgender background occurred both before, during, and after transition. The increased vulnerability of the transgender group is described in many other reports (Lombardi, 2002; Public Health Agency of Sweden, 2015).

Interpretations of suicidality and increased psychiatric morbidity

How to interpret the high prevalence of psychiatric morbidity and suicidality both before and after gender-affirming treatment is the subject of an ongoing debate. By and large, it is either seen as a failure of gender-affirming treatment or caused by minority status stress. Those interpreting it as a failure of gender-affirming treatment argue that the treatment does not improve mental health, or that suicide or suicide attempts may be signs of regret (Levine, 2016; Zucker et al., 2016). However, the most common risk factors for suicide and suicide attempts are mood disorders and substance abuse, as well as sociodemographic risk factors (Nock et al., 2008). The prevalence of mood disorder is high prior to gender-affirming treatment (Dhejne et al., 2016; Heylens, et al., 2014a). Gender-affirming treatment reduces mental health problems caused by gender dysphoria, but mental health problems with another origin will persist, if not also treated.

Another line of reasoning explains the increased mental health issues with the minority stress model (Meyer, 2003). Stigma, prejudice including internalized transphobia, and discrimination

add stress, which causes an increase in mental health disparities. Resilience, coping, and social support can balance the stress, and the model describes the impact on health as a net outcome of negative stress and positive processes (Bauer, Scheim, Pyne, Travers, & Hammond, 2015; Bockting et al., 2016b; Davey et al., 2014). In support of the minority stress model, we found an association between immigrant background and not being accepted by others in assigned gender. We were unable to detect any association with known protectors, as other have done (Davey et al., 2014; Nuttbrock et al., 2012), however this may be due to a too small sample.

A third way of addressing the high prevalence of mental health problems in the transgender group is to look at models used for explaining psychiatric morbidity in cisgender populations. The background to psychiatric morbidity is today seen as function of genetic vulnerability and stress factors. Examples of stress factors could be childhood adversities, somatic diseases, drug use, and loss of important persons or economy. A recent report from the WHO, the World Mental Health Survey in 21 countries (high, middle and low income) concluded that childhood adversities had a strong association with all lifetime psychiatric disorders (DSM-IV) (Nock et al., 2008). In Study IV we found that childhood adversities were associated with current psychiatric morbidity. Similar association between depression/ anxiety disorder and childhood maltreatment has been reported from Spain and Italy (Bandini et al., 2011; Bergero-Miguel et al., 2016). It is not known whether gender dysphoria is also associated with a genetic vulnerability for psychiatric morbidity.

Implications

Future studies on outcome after gender-affirming treatment would benefit from a valid strong outcome measure of gender dysphoria/gender incongruence (Arcelus & Bouman, 2015). The high mortality and high rate of mental illness including suicidality stress the vulnerability of this group and the importance of improved health care. Gender dysphoric individuals with co-occurrence of psychiatric disorder should be offered the same psychiatric treatment as cisgender individuals. Mainstream psychiatric care needs to be aware that transgender people are at risk for suicide and suicide attempts, and needs to increase their knowledge of transgender medicine and transgender awareness. Since stigma, discrimination, and abuse are common in the transgender group it is important that the health care system collectively – but also individuals in the system – does not add to the negative stressors. One way to reduce the risk that the health care *per se* induces stress is by working together with the transgender population and their organizations to improve care.

6 ON THE IMPACT OF RESEARCH FINDINGS

Researchers are happy if their findings are recognized and have an impact. However, once published, the researcher loses control of how results are used. Study III is the first long-term cohort study of mortality and psychiatric inpatient care following gender transition (Dhejne et al., 2011). This paper has also had an impact outside the scientific world. Our findings have been used to argue that gender-affirming treatment should be stopped since it could be dangerous (Levine, 2016). But the results have also been used to show the vulnerability of the group and that better transgender health care is needed (Arcelus & Bouman, 2015; Zeluf et al., 2016). Despite the paper clearly stating that the study is not designed to evaluate whether or not gender-affirming is beneficial, it has been interpreted as such. But we do not know what would have happened without gender-affirming treatment; the situation may have been even worse. As an analogy, similar studies have found increased somatic morbidity, suicide rates, and overall mortality for patients treated for depression and bipolar disorder (Ösby, Brandt, Correia, Ekbom, & Sparen, 2001). This is important information, but it does not follow that antidepressant or mood stabilizing treatment cause the mortality. Most of the articles that use the study to argue against gender-affirming health care are published in non-peer reviewed papers and the public media in general. These non-scientific publications are difficult to keep track of. I am grateful to friends, colleagues, patients, LGBT organizations, and journalists who have alerted me when the results of the study have been misinterpreted, giving me a possibility to respond to the authors. One could argue that the results should never have been published due to the hurt caused to transgender persons. However, not publishing the results would also hurt the transgender group and take away an opportunity to receive better health care.

7 FINAL REMARKS

A cisgender person may have difficulty in comprehending the situation for a person with gender dysphoria. We need to train in strategies to cope with our spontaneous emotional reactions professionally, when challenged with something unfamiliar. This is something that is a general part of health care providers' professional education and training, though in relation to situations where fundamental aspects of the gender binary dogma are questioned it is natural to react emotionally and leave the paradigm of evidence-based care. In such a situation, stringent separation of scientifically-based knowledge from spontaneous opinions or opinions based on religious, political, or other platforms is vital but not always given. Once transgender individuals are no longer seen as exotic and aberrant, but rather as regular members of society there will be general and mental health benefits as well as a reduction in all-cause mortality (Arcelus & Bouman, 2015).

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9 REFERENCES

Abraham, F. (1931). Genitalomwandlung an zwei maennlichen Transvestiten. *Zeitchrift fur Sexualwissenschaft und Sexualpolitik, 18*, 223-226.

American Psychiatric Association. (1980). *Diagnostic and statistical manual of mental disorders (3rd ed.)*. Washington, DC: Author.

American Psychiatric Association. (1987). *Diagnostic and statistical manual of mental disorders (3rd ed., rev.)*. Washington, DC: Author.

American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders,(4th ed.)*. Washington, DC: Author.

American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders, (4th ed., text rev.)*. Washington, DC: Author.

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders, (5th ed.)*. Arlington, VA: Author.

Anchersen, P. (1956). Problems of transvestism. *Acta Psychiatrica et Neurologica Scandinavica. Supplementum, 106*, 249-256.

Andersen, J. P., & Blosnich, J. (2013). Disparities in adverse childhood experiences among sexual minority and heterosexual adults: results from a multi-state probability-based sample. *PloS One, 8*(1), e5469. doi: 10.1371/journal.pone.0054691

Arcelus, J., & Bouman, W. P. (2015). Current and Future Direction of Gender Dysphoria and Gender Incongruence Research. *Journal of Sexual Medicine, 12*(12), 2226-2228. doi:10.1111/jsm.13065

Arcelus, J., Bouman, W. P., Van Den Noortgate, W., Claes, L., Witcomb, G., & Fernandez-Aranda, F. (2015). Systematic review and meta-analysis of prevalence studies in transsexualism. *European Psychiatry*. doi:10.1016/j.eurpsy.2015.04.005

Asscheman, H., Giltay, E. J., Megens, J. A., de Ronde, W. P., van Trotsenburg, M. A., & Gooren, L. J. (2011). A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. *European Journal of Endocrinology of the European Federation of Endocrine Societies, 164*(4), 635-642. doi:10.1530/eje-10-1038

Auer, M. K., Fuss, J., Hohne, N., Stalla, G. K., & Sievers, C. (2014). Transgender transitioning and change of self-reported sexual orientation. *PloS One, 9*(10), e110016. doi:10.1371/journal.pone.0110016

Auer, M. K., Höhne, N., Bazarra-Castro, M. Á., Pfister, H., Fuss, J., & Stalla, G. K. (2013). Psychopathological profiles in transsexuals and the challenge of their special status among the sexes. *PloS One, 8*(10), e78469. doi:10.1371/journal.pone.0078469

Baba, T., Endo, T., Ikeda, K., Shimizu, A., Honnma, H., Ikeda, H., . . . Saito, T. (2011). Distinctive Features of Female-to-Male Transsexualism and Prevalence of Gender Identity Disorder in Japan. *The Journal of Sexual Medicine, 8*(6), 1686-1693. doi:10.1111/j.1743-6109.2011.02252.x

Bakker, A., van Kesteren, P. J. M., Gooren, L. J. G., & Bezemer, P. D. (1993). The prevalence of transsexualism in the Netherlands. *Acta Psychiatrica Scandinavica, 87*(4), 237-238. doi:10.1111/j.1600-0447.1993.tb03364.x

Bandini, E., Fisher, A. D., Ricca, V., Ristori, J., Meriggiola, M. C., Jannini, E. A., . . . Maggi, M. (2011). Childhood maltreatment in subjects with male-to-female gender identity disorder. *International Journal of Impotence Research, 23*(6), 276-285. doi:10.1038/ijir.2011.39

Bao, A. M., & Swaab, D. F. (2011). Sexual differentiation of the human brain: relation to gender identity, sexual orientation and neuropsychiatric disorders. *Frontiers in Neuroendocrinology, 32*(2), 214-226. doi:10.1016/j.yfrne.2011.02.007

Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., & Clubley, E. (2001). The autism-spectrum quotient (AQ): evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *Journal of Autism and Developmental Disorders, 31*(1), 5-17.

Bauer, G. R., Scheim, A. I., Pyne, J., Travers, R., & Hammond, R. (2015). Intervenable factors associated with suicide risk in transgender persons: a respondent driven sampling study in Ontario, Canada. *BMC Public Health, 15*, 525. doi:10.1186/s12889-015-1867-2

Beek, T.F., Kreukels, B.P. C., Cohen-Kettenis, P.T., & Steensma, T.D. (2015). Partial Treatment Requests and Underlying Motives of Applicants for Gender Affirming Interventions. *The Journal of Sexual Medicine, 12*(11), 2201-2205. doi:http://dx.doi.org/10.1111/jsm.13033

Bell, E. C., Willson, M. C., Wilman, A. H., Dave, S., & Silverstone, P. H. (2006). Males and females differ in brain activation during cognitive tasks. *Neuroimage, 30*(2), 529-538. doi:10.1016/j.neuroimage.2005.09.049

Benjamin, H. (1966). *The transexual phenomenon*. New York: Julian Press.

Bentz, E-K., Hefler, L. A., Kaufmann, U., Huber, J. C., Kolbus, A., & Tempfer, C. B. (2008). A polymorphism of the CYP17 gene related to sex steroid metabolism is associated with female-to-male but not male-to-female transsexualism. *Fertility and Sterility, 90*(1), 56-59. doi:http://dx.doi.org/10.1016/j.fertnstert.2007.05.056

Bergero-Miguel, T., Garcia-Encinas, M. A., Villena-Jimena, A., Perez-Costillas, L., Sanchez-Alvarez, N., de Diego-Otero, Y., & Guzman-Parra, J. (2016). Gender Dysphoria and Social Anxiety: An Exploratory Study in Spain. *Journal of Sexual Medicine, 13*(8), 1270-1278. doi:10.1016/j.jsxm.2016.05.009

Berglund, H., Lindström, P., & Savic, I. (2006). Brain response to putative pheromones in lesbian women. *Proceedings of the National Academy of Sciences of the United States of America, 103*(21), 8269-8274. doi:10.1073/pnas.0600331103

Bergman, H., & Källmén, H. (2002). Alcohol use among Swedes and a psychometric evaluation of the Alcohol Use Disorders Identification Test *Alcohol and Alcoholism, 37*(3), 245-251.

Berli, J.U., Knudson, G., Fraser, L., Tangpricha, V., Ettner, R., Ettner, F.M., . . . Schechter, L. (2017). What Surgeons Need to Know About Gender Confirmation Surgery When Providing Care for Transgender Individuals: A Review. *JAMA Surg*. doi:10.1001/jamasurg.2016.5549

Berman, A. H., Wennberg, P., & Källmén, H. (2012). *AUDIT & DUDIT. Identifiera problem med alkohol och droger*. Stockholm: Gothia Förlag.

Björkenstam E, Burström B, Vinnerljung B, Kosidou K. (2016). Childhood adversity and psychiatric disorder in young adulthood: An analysis of 107,704 Swedes. *Journal of Psychiatry Research77*:67-75. doi:10.1016/j.jpsychires.2016.02.018

Blanchard, R. (1985). Typology of male-to-female transsexualism. *Archives of Sexual Behavior, 14*(3), 247-261. doi:10.1007/bf01542107

Blanchard, R., Clemmensen, L. H., & Steiner, B. W. (1987). Heterosexual and homosexual gender dysphoria. *Archives of Sexual Behavior, 16*(2), 139-152.

Blanchard, R. (1989). The classification and labeling of nonhomosexual gender dysphorias. *Archives of Sexual Behavior, 18*(4), 315-334. doi:10.1007/bf01541951

Blanchard, R., & Sheridan, P. M. (1992). Sibship size, sibling sex ratio, birth order, and parental age in homosexual and nonhomosexual gender dysphorics. *Journal of Nervous and Mental Disease, 180*(1), 40-47.

Blanchard, R., Zucker, K. J., Cohen-Kettenis, P. T., Gooren, L. J., & Bailey, J. M. (1996). Birth order and sibling sex ratio in two samples of Dutch gender-dysphoric homosexual males. *Archives of Sexual Behavior, 25*(5), 495-514.

Blanchard, R. (2005). Early History of the Concept of Autogynephilia. *Archives of Sexual Behavior, 34*(4), 439-446. doi:10.1007/s10508-005-4343-8

Blosnich, J. R., Brown, G. R., Wojcio, S., Jones, K. T., & Bossarte, R. M. (2014). Mortality Among Veterans with Transgender-Related Diagnoses in the Veterans Health Administration, FY2000-2009. *LGBT Health, 1*(4), 269-276. doi:10.1089/lgbt.2014.0050

Bockting, W. O. , Knudson, G., & Goldberg, J. M. (2006). Counseling and Mental Health Care for Transgender Adults and Loved Ones *International Journal of Transgenderism, 9*(3-4), 35-82. doi:10.1300/J485v09n03_03

Bockting, W.O. (2008). Psychotherapy and the real-life experience: from gender dichotomy to gender diversity. *Sexologies, 17*, 211-224.

Bockting, W. O., Miner, M. H., Swinburne Romine, R. E., Hamilton, A., & Coleman, E. (2013). Stigma, mental health, and resilience in an online sample of the US transgender population. *American Journal of Public Health, 103*(5), 943-951. doi:10.2105/ajph.2013.301241

Bockting, W. O. (2016a). Vulnerability and Resilience Among Gender-Nonconforming Children and Adolescents: Mental Health Professionals Have a Key Role to Play. *Journal of the American Academy of Child and Adolescent Psychiatry, 55*(6), 441-443. doi:10.1016/j.jaac.2016.04.008

Bockting, W., Coleman, E., Deutsch, M. B., Guillamon, A., Meyer, I., Meyer, W., 3rd, . . . Ettner, R. (2016b). Adult development and quality of life of transgender and gender nonconforming people. *Current Opinion in Endocrinology, Diabetes, and Obesity, 23*(2), 188-197. doi:10.1097/med.0000000000000232

Bodlund, O., Kullgren, G., Sundbom, E., & Höjerback, T. (1993). Personality traits and disorders among transsexuals. *Acta Psychiatrica Scandinavica, 88*(5), 322-327. doi:10.1111/j.1600-0447.1993.tb03467.x

Bodlund, O., & Kullgren, G. (1996). Transsexualism--general outcome and prognostic factors: a five-year follow-up study of nineteen transsexuals in the process of changing sex. *Archives of Sexual Behavior, 25*(3), 303-316.

Bohn, M. J., Babor, T. B., & Kranzler, H. R. (1995). The Alcohol Use Disorders Identification Test (AUDIT): validation of a screening instrument for use in medical settings. *Journal of Studies on Alcohol, 56*(4), 423–432. doi:http://dx.doi.org/10.15288/jsa.1995.56.423

Borras, L., Huguelet, P., & Eytan, A. (2007). Delusional "pseudotranssexualism" in schizophrenia. *Psychiatry, 70*(2), 175-179. doi:10.1521/psyc.2007.70.2.175

Bouman, W.P., Schwend, A.S., Motmans, J., Smiley, A., Safer, J.D., Deutsch, M.B., . . . Winter, S. (2016). Language and trans health. *International Journal of Transgenderism*, 1-6. doi:10.1080/15532739.2016.1262127

Bozkurt, A., Bozkurt, O. H., & Sonmez, I. (2015). Birth Order and Sibling Sex Ratio in a Population with High Fertility: Are Turkish Male to Female Transsexuals Different? *Archives of Sexual Behavior, 44*(5), 1331-1337. doi:10.1007/s10508-014-0425-9

Brown, G. R., & Jones, K. T. (2015). Health Correlates of Criminal Justice Involvement in 4,793 Transgender Veterans. *LGBT Health, 2*(4), 297-305. doi:10.1089/lgbt.2015.0052

Bruffaerts, R., Demyttenaere, K., Borges, G., Haro, J. M., Chiu, W. T., Hwang, I., . . . Nock, M. K. (2010). Childhood adversities as risk factors for onset and persistence of suicidal behaviour. *British Journal of Psychiatry, 197*(1), 20-27. doi:10.1192/bjp.bp.109.074716

Burke, S. M., Cohen-Kettenis, P. T., Veltman, D. J., Klink, D. T., & Bakker, J. (2014). Hypothalamic response to the chemo-signal androstadienone in gender dysphoric children and adolescents. *Frontiers in Endocrinology, 5*, 60. doi:10.3389/fendo.2014.00060

Burns, A., Farrell, M., & Brown, J. C. (1990). Clinical features of patients attending a gender-identity clinic. *British Journal of Psychiatry, 157*, 265-268.

Byne, W., Lasco, M.S., Kemether, E., Shinwari, A., Edgar, M.A, Morgello, S., & Tobet, S. (2000). The interstitial nuclei of the human anterior hypothalamus: an investigation of sexual variation in volume and cell size, number and density. *Brain Research Bulletin, 856*(1–2), 254–258.

Caudwell, D.O. (1949). Psychopatia Transsexualis. *Sexology, 16,* 274-280.

Center of Excellence for Transgender Health. (2016). Primary Care Protocol for Transgender Patient Care. Retrieved from http://www.transhealth.ucsf.edu/trans?page=guidelines-terminology website

Cerwenka, S., Nieder, T. O., Cohen-Kettenis, P., De Cuypere, G., Haraldsen, I. R., Kreukels, B. P., & Richter-Appelt, H. (2014). Sexual behavior of gender-dysphoric individuals before gender-confirming interventions: a European multicenter study. *Journal of Sex and Marital Therapy, 40*(5), 457-471. doi:10.1080/0092623x.2013.772550

Chen, L. P., Murad, M. H., Paras, M. L., Colbenson, K. M., Sattler, A. L., Goranson, E. N., . . . Zirakzadeh, A. (2010). Sexual Abuse and Lifetime Diagnosis of Psychiatric Disorders: Systematic Review and Meta-analysis. *Mayo Clinic Proceedings, 85*(7), 618-629. doi:http://dx.doi.org/10.4065/mcp.2009.0583

Claes, L., Bouman, W. P., Witcomb, G., Thurston, M., Fernandez-Aranda, F., & Arcelus, J. (2015). Non-suicidal self-injury in trans people: associations with psychological symptoms, victimization, interpersonal functioning, and perceived social support. *Journal of Sexual Medicine, 12*(1), 168-179. doi:10.1111/jsm.12711

Clements-Nolle, K., Marx, R., & Katz, M. (2006). Attempted suicide among transgender persons: The influence of gender-based discrimination and victimization. *Journal of Homosexuality, 51*(3), 53-69. doi:10.1300/J082v51n03_04

Cohen-Kettenis, P. T., & Gooren, L. J. G. (1999). Transsexualism: A review of etiology, diagnosis and treatment. *Journal of Psychosomatic Research, 46*(4), 315-333. doi:http://dx.doi.org/10.1016/S0022-3999(98)00085-3

Cohen-Kettenis, P. T., Owen, A., Kaijser, V. G., Bradley, S. J., & Zucker, K. J. (2003). Demographic characteristics, social competence, and behavior problems in children with gender identity disorder: a cross-national, cross-clinic comparative analysis. *Journal of Abnormal Child Psychology, 31*(1), 41-53.

Cohen-Kettenis, P. T., & Pfäfflin, F. (2010). The DSM diagnostic criteria for gender identity disorder in adolescents and adults. *Archives of Sexual Behavior, 39*(2), 499-513. doi:10.1007/s10508-009-9562-y

Coleman, E., Colgan, P., & Gooren, L. (1992). Male cross-gender behavior in Myanmar (Burma): a description of the acault. *Archives of Sexual Behavior, 21*(3), 313-321.

Coleman, E., Bockting, W., Botzer, M., Cohen-Kettenis, P. T., DeCuypere, G., Feldman, J., . . . Zucker, K. (2012). Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People, Version 7. *International Journal of Transgenderism, 13*(4), 165-232. doi:10.1080/15532739.2011.700873

Colizzi, M., Costa, R., Pace, V., & Todarello, O. (2013). Hormonal treatment reduces psychobiological distress in gender identity disorder, independently of the attachment style. *Journal of Sexual Medicine, 10*(12), 3049-3058. doi:10.1111/jsm.12155

Colizzi, M., Costa, R., & Todarello, O. (2014). Transsexual patients' psychiatric comorbidity and positive effect of cross-sex hormonal treatment on mental health: results from a longitudinal study. *Psychoneuroendocrinology, 39*, 65-73. doi:10.1016/j.psyneuen.2013.09.029

Colizzi, M., Costa, R., Scaramuzzi, F., Palumbo, C., Tyropani, M., Pace, V., . . . Todarello, O. (2015). Concomitant psychiatric problems and hormonal treatment induced metabolic syndrome in gender dysphoria individuals: a 2 year follow-up study. *Journal of Psychosomatic Research, 78*(4), 399-406. doi:10.1016/j.jpsychores.2015.02.001

Corliss, H. L., Cochran, S. D., & Mays, V. M. (2002). Reports of parental maltreatment during childhood in a United States population-based survey of homosexual, bisexual, and heterosexual adults. *Child Abuse and Neglect, 26*(11), 1165-1178. doi:http://dx.doi.org/10.1016/S0145-2134(02)00385-X

Cosgrove, K. P., Mazure, C. M., & Staley, J. K. (2007). Evolving Knowledge of Sex Differences in Brain Structure, Function, and Chemistry. *Biological Psychiatry, 62*(8), 847-855. doi:http://dx.doi.org/10.1016/j.biopsych.2007.03.001

Davey, A., Bouman, W. P., Meyer, C., & Arcelus, J. (2014). Social Support and Psychological Well-Being in Gender Dysphoria: A Comparison of Patients With Matched Controls. *The Journal of Sexual Medicine, 11*(12), 2976-2985. doi:10.1111/jsm.12681

Davey, A., Arcelus, J., Meyer, C., & Bouman, W. P. (2016). Self-injury among trans individuals and matched controls: prevalence and associated factors. *Health Soc Care Community, 24*(4), 485-494. doi:10.1111/hsc.12239

Davies, W., & Wilkinson, L. S. (2006). It is not all hormones: alternative explanations for sexual differentiation of the brain. *Brain Research, 1126*(1), 36-45. doi:10.1016/j.brainres.2006.09.105

De Cuypere, G., Janes, C., & Rubens, R. (1995). Psychosocial functioning of transsexuals in Belgium. *Acta Psychiatrica Scandinavica, 91*(3), 180-184.

De Cuypere, G., T'Sjoen, G., Beerten, R., Selvaggi, G., De Sutter, P., Hoebeke, P., . . . Rubens, R. (2005). Sexual and physical health after sex reassignment surgery. *Archives of Sexual Behavior, 34*(6), 679-690. doi:10.1007/s10508-005-7926-5

De Cuypere, G., Elaut, E., Heylens, G., Van Maele, G. , Selvaggi, G, T'Sjoen, G., . . . Monstrey, S. (2006). Long-term follow-up: psychosocial outcome of Belgian transsexuals after sex reassignment surgery. *Sexologies 15*, 126-133. doi:10.1016/j.sexol.2006.04.002

De Cuypere, G., Van Hemelrijck, M., Michel, A., Carael, B., Heylens, G., Rubens, R., . . . Monstrey, S. (2007). Prevalence and demography of transsexualism in Belgium. *European Psychiatry, 22*(3), 137-141. doi:S0924-9338(06)00180-5 [pii]10.1016/j.eurpsy.2006.10.002

de Vries, A. L., Doreleijers, T. A., Steensma, T. D., & Cohen-Kettenis, P. T. (2011). Psychiatric comorbidity in gender dysphoric adolescents. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 52*(11), 1195-1202. doi:10.1111/j.1469-7610.2011.02426.x

de Vries, A. L., McGuire, J. K., Steensma, T. D., Wagenaar, E. C., Doreleijers, T. A., & Cohen-Kettenis, P. T. (2014). Young adult psychological outcome after puberty suppression and gender reassignment. *Pediatrics, 134*(4), 696-704. doi:10.1542/peds.2013-2958

Devor, H. . (1994). Transsexualism, Dissociation, and Child Abuse: An Initial Discussion Based on Nonclinical Data. *Journal of Psychology and Human Sexuality, 6*(3), 49-72.

Dhejne, C., Lichtenstein, P., Boman, M., Johansson, A. L., Langstrom, N., & Landén, M. (2011). Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. *PloS One, 6*(2), e16885. doi:10.1371/journal.pone.0016885

Dhejne, C., & Arver, S. (2012). *Handbook of clinical Gender Medicine, Chapter Transsexualism* (K. Schenk-Gustafsson, DeCola, P.R., Pfaff, D.W., Pisetsky, D.S. Ed.). Basel: Karger.

Dhejne, C., Öberg, K., Arver, S., & Landén, M. (2014). An analysis of all applications for sex reassignment surgery in Sweden, 1960-2010: prevalence, incidence, and regrets. *Archives of Sexual Behavior, 43*(8), 1535-1545. doi:10.1007/s10508-014-0300-8

Dhejne, C., Van Vlerken, R., Heylens, G., & Arcelus, J. (2016). Mental health and gender dysphoria: A review of the literature. *International Review of Psychiatry, 28*(1), 44-57. doi:10.3109/09540261.2015.1115753

Diamond, M., & Sigmundson, H. K. (1997). Sex reassignment at birth. Long-term review and clinical implications. *Archives of Pediatrics and Adolescent Medicine, 151*(3), 298-304.

Dixen, J. M., Maddever, H., Van Maasdam, J., & Edwards, P. W. (1984). Psychosocial characteristics of applicants evaluated for surgical gender reassignment. *Archives of Sexual Behavior, 13*(3), 269-276. doi:10.1007/bf01541653

Dolan, J.D. (1987). Transsexualism: syndrome or symptom? *Canadian Journal of Psychiatry, 32*(8), 666-673.

Doorn, C. D., Poortinga, J., & Verschoor, A. M. (1994). Cross-gender identity in transvestites and male transsexuals. *Archives of Sexual Behavior, 23*(2), 185-201.

Drescher, J., Cohen-Kettenis, P., & Winter, S. (2012). Minding the body: situating gender identity diagnoses in the ICD-11. *International Review of Psychiatry, 24*(6), 568-577. doi:10.3109/09540261.2012.741575

Drescher, Jack. (2013). Controversies in Gender Diagnoses. *LGBT Health, 1*(1), 10-14. doi:10.1089/lgbt.2013.1500

Duisin, D., Batinic, B., Barisic, J., Djordjevic, M. L., Vujovic, S., & Bizic, M. (2014). Personality disorders in persons with gender identity disorder. *ScientificWorldJournal, 2014*, 809058. doi:10.1155/2014/809058

Dulko, S., & Imielinski, C. (2004). The epidemiology of transsexualism in Poland. *Journal of Psychosomatic Research, 56*, 637.

Eklund, P. L., Gooren, L. J., & Bezemer, P. D. (1988). Prevalence of transsexualism in The Netherlands. *British Journal of Psychiatry, 152*, 638-640.

Elbe, L. (1933). *Man into Woman: The first Sex Change* (N Hoeyer Ed.). London: Blue Boat Books.

Eldh, J., Berg, A., & Gustafsson, M. (1997). Long-term follow up after sex reassignment surgery. *Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery, 31*(1), 39-45.

Ellis, H. (1928). *Studies in the Psychology of Sex. Part II, Eonism*. Philadelphia

Evans, E., Hawton, K., & Rodham, K. (2005). Suicidal phenomena and abuse in adolescents: a review of epidemiological studies. *Child Abuse and Neglect, 29*(1), 45-58. doi:http://dx.doi.org/10.1016/j.chiabu.2004.06.014

Feldman, J., Brown, G. R., Deutsch, M. B., Hembree, W., Meyer, W., Meyer-Bahlburg, H. F., . . . Safer, J. D. (2016). Priorities for transgender medical and healthcare research. *Current Opinion in Endocrinology, Diabetes, and Obesity, 23*(2), 180-187. doi:10.1097/med.0000000000000231

Fernandez, R., Esteva, I., Gomez-Gil, E., Rumbo, T., Almaraz, M. C., Roda, E., . . . Pasaro, E. (2014a). Association study of ERbeta, AR, and CYP19A1 genes and MtF transsexualism. *Journal of Sexual Medicine, 11*(12), 2986-2994. doi:10.1111/jsm.12673

Fernandez, R., Esteva, I., Gomez-Gil, E., Rumbo, T., Almaraz, M. C., Roda, E., . . . Pasaro, E. (2014b). The (CA)n polymorphism of ERbeta gene is associated with FtM transsexualism. *Journal of Sexual Medicine, 11*(3), 720-728. doi:10.1111/jsm.12398

Fernandez, R., Cortes-Cortes, J., Esteva, I., Gomez-Gil, E., Almaraz, M. C., Lema, E., . . . Pasaro, E. (2015). The CYP17 MspA1 Polymorphism and the Gender Dysphoria. *Journal of Sexual Medicine, 12*(6), 1329-1333. doi:10.1111/jsm.12895

Feusner, J. D., Dervisic, J., Kosidou, K., Dhejne, C., Bookheimer, S., & Savic, I. (2016a). Female-to-Male Transsexual Individuals Demonstrate Different Own Body Identification. *Archives of Sexual Behavior, 45*(3), 525-536. doi:10.1007/s10508-015-0596-z

Feusner, J. D., Lidström, A., Moody, T. D., Dhejne, C., Bookheimer, S. Y., & Savic, I. (2016b). Intrinsic network connectivity and own body perception in gender dysphoria. *Brain Imaging Behav*. doi:10.1007/s11682-016-9578-6

Fisher, A. D., Bandini, E., Casale, H., Ferruccio, N., Meriggiola, M. C., Gualerzi, A., . . . Maggi, M. (2013). Sociodemographic and clinical features of gender identity disorder: an Italian multicentric evaluation. *Journal of Sexual Medicine, 10*(2), 408-419. doi:10.1111/j.1743-6109.2012.03006.x

Fisher, A. D., Castellini, G., Bandini, E., Casale, H., Fanni, E., Benni, L., . . . Rellini, A. H. (2014). Cross-Sex Hormonal Treatment and Body Uneasiness in Individuals with Gender Dysphoria. *The Journal of Sexual Medicine, 11*(3), 709-719. doi:10.1111/jsm.12413

Fisk, N.M. (1974). Gender dysphoria syndrome: The conceptualization that liberalizes indications for total gender reorientation and implies a broadly based multi-dimensional rehabilitative regimen-Editorial comment on male transsexualism. *Western Journal of Medicine, 120*, 386-391.

Frackowiak, R. S. (2004). *Human brain function*. London: Elsevier Academic.

Fraser, L., & Knudson, G. (2017). Past and Future Challenges Associated with Standards of Care for Gender Transitioning Clients. *Psychiatric Clinics of North America, 40*(1), 15-27. doi:10.1016/j.psc.2016.10.012

Frings, L., Wagner, K., Unterrainer, J., Spreer, J., Halsband, U., & Schulze-Bonhage, A. (2006). Gender-related differences in lateralization of hippocampal activation and cognitive strategy. *Neuroreport, 17*(4), 417-421. doi:10.1097/01.wnr.0000203623.02082.e3

Friston, K. J., Holmes, A., Poline, J. B., Price, C. J., & Frith, C. D. (1996). Detecting activations in PET and fMRI: levels of inference and power. *Neuroimage, 4*(3 Pt 1), 223-235. doi:10.1006/nimg.1996.0074

Friston, K. J., Holmes, A. P., & Worsley, K. J. (1999). How many subjects constitute a study? *Neuroimage, 10*(1), 1-5. doi:10.1006/nimg.1999.0439

Garrels, L., Kockott, G., Michael, N., Preuss, W., Renter, K., Schmidt, G., . . . Windgassen, K. (2000). Sex ratio of transsexuals in Germany: the development over three decades. *Acta Psychiatrica Scandinavica, 102*(6), 445-448.

Gehring, D., & Knudson, G. (2005). Prevalence of Childhood Trauma in a Clinical Population of Transsexual People. *International Journal of Transgenderism, 8*(1), 23-30. doi:10.1300/J485v08n01_03

Glidden, D., Bouman, W. P., Jones, B. A., & Arcelus, J. (2016). Gender Dysphoria and Autism Spectrum Disorder: A Systematic Review of the Literature. *Sex Med Rev, 4*(1), 3-14. doi:10.1016/j.sxmr.2015.10.003

Godlewski, J. (1988). Transsexualism and anatomic sex ratio reversal in Poland. *Archives of Sexual Behavior, 17*(6), 547-548.

Gomez Gil, E., Trilla Garcia, A., Godas Sieso, T., Halperin Rabinovich, I., Puig Domingo, M., Vidal Hagemeijer, A., & Peri Nogues, J. M. (2006). [Estimation of prevalence, incidence and sex ratio of transsexualism in Catalonia according to health care demand]. *Actas Españolas de Psiquiatría: Acepsi, 34*(5), 295-302.

Gomez-Gil, E., Vidal-Hagemeijer, A., & Salamero, M. (2008). MMPI-2 characteristics of transsexuals requesting sex reassignment: comparison of patients in prehormonal and presurgical phases. *Journal of Personality Assessment, 90*(4), 368-374. doi:10.1080/00223890802108022

Gomez-Gil, E., Trilla, A., Salamero, M., Godas, T., & Valdes, M. (2009). Sociodemographic, clinical, and psychiatric characteristics of transsexuals from Spain. *Archives of Sexual Behavior, 38*(3), 378-392. doi:10.1007/s10508-007-9307-8

Gómez-Gil, E., Esteva, I., Carrasco, R., Almaraz, M. C., Pasaro, E., Salamero, M., & Guillamon, A. (2011). Birth Order and Ratio of Brothers to Sisters in Spanish Transsexuals. *Archives of Sexual Behavior, 40*(3), 505-510. doi:10.1007/s10508-010-9614-3

Gooren, L. J., Giltay, E. J., & Bunck, M. C. (2008). Long-term treatment of transsexuals with cross-sex hormones: extensive personal experience. *Journal of Clinical Endocrinology and Metabolism, 93*(1), 19-25. doi:jc.2007-1809 [pii] 10.1210/jc.2007-1809

Gorin-Lazard, A., Baumstarck, K., Boyer, L., Maquigneau, A., Penochet, J. C., Pringuey, D., . . . Auquier, P. (2013). Hormonal therapy is associated with better self-esteem, mood, and quality of life in transsexuals. *Journal of Nervous and Mental Disease, 201*(11), 996-1000. doi:10.1097/NMD.0000000000000046

Green, R., Stoller, R. J., & Mac Andrew, C. (1966). Attitudes toward sex transformation procedures. *Archives of General Psychiatry, 15*(2), 178-182.

Green, R (1969). *Transsexualism: Mythological, historical and cross-cultural aspects, in Transsexualism and Sex Reassignment* (R. Green & J. Money Eds.). Baltimore: John Hopkins University Press,.doi:10.1001/archpsyc.1966.01730140066011

Green, R. (1974). *Sexual identity conflict in children and adults*. New York: Basic Books.

Green, R. (2000). Birth order and ratio of brothers to sisters in transsexuals. *Psychological Medicine, 30*(4), 789-795.

Hage, J. J., Karim, R. B., & Laub, D. R. (2007). On the origin of pedicled skin inversion vaginoplasty: life and work of Dr Georges Burou of Casablanca. *Annals of Plastic Surgery, 59*(6), 723-729. doi:10.1097/01.sap.0000258974.41516.bc

Hahn, A., Kranz, G. S., Kublbock, M., Kaufmann, U., Ganger, S., Hummer, A., . . . Lanzenberger, R. (2015). Structural Connectivity Networks of Transgender People. *Cerebral Cortex, 25*(10), 3527-3534. doi:10.1093/cercor/bhu194

Hamburger, C., Stürup, G. K., & Dahl-Iversen, E. E. (1953a). Transvestism: Hormonal, psychiatric, and surgical treatment. *Journal of the American Medical Association, 152*(5), 391-396. doi:10.1001/jama.1953.03690050015006

Hamburger, C. (1953b). The desire for change of sex as shown by personal letters from 465 men and women. *Acta Endocrinologica, 14*(4), 361-375. doi:10.1530/acta.0.0140361

Haraldsen, I. R., & Dahl, A. A. (2000). Symptom profiles of gender dysphoric patients of transsexual type compared to patients with personality disorders and healthy adults. *Acta Psychiatrica Scandinavica, 102*(4), 276-281.

Hare, L., Bernard, P., Sanchez, F. J., Baird, P. N., Vilain, E., Kennedy, T., & Harley, V. R. (2009). Androgen receptor repeat length polymorphism associated with male-to-female transsexualism. *Biological Psychiatry, 65*(1), 93-96. doi:10.1016/j.biopsych.2008.08.033

Hembree, W. C., Cohen-Kettenis, P., Delemarre-van de Waal, H. A., Gooren, L. J., Meyer, W. J., 3rd, Spack, N. P., . . . Montori, V. M. (2009). Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology Metabolism, 94*(9), 3132-3154. doi:10.1210/jc.2009-0345 jc.2009-0345 [pii]

Henningsson, S., Westberg, L., Nilsson, S., Lundstrom, B., Ekselius, L., Bodlund, O., . . . Landén, M. (2005). Sex steroid-related genes and male-to-female transsexualism. *Psychoneuroendocrinology, 30*(7), 657-664. doi:S0306-4530(05)00045-4 [pii]10.1016/j.psyneuen.2005.02.006

Hepp, U., Kraemer, B., Schnyder, U., Miller, N., & Delsignore, A. (2005). Psychiatric comorbidity in gender identity disorder. *Journal of Psychosomatic Research, 58*(3), 259-261. doi:10.1016/j.jpsychores.2004.08.010

Herdt, G. (1994). *Third sex, third gender: Beyond sexual dimorphism in culture and history* (G. Herdt Ed.). New Yoork: Zone books.

Hertz, J., Tillinger, K-G., & Westman, A. (1961). TRANSVESTITISM. *Acta Psychiatrica Scandinavica, 37*(4), 283-294. doi:10.1111/j.1600-0447.1961.tb07363.x

Heylens, G., De Cuypere, G., Zucker, K. J., Schelfaut, C., Elaut, E., Vanden Bossche, H., . . . T'Sjoen, G. (2012). Gender identity disorder in twins: a review of the case report literature. *Journal of Sexual Medicine, 9*(3), 751-757. doi:10.1111/j.1743-6109.2011.02567.x

Heylens, G., Elaut, E., Kreukels, B. P., Paap, M. C., Cerwenka, S., Richter-Appelt, H., . . . De Cuypere, G. (2014a). Psychiatric characteristics in transsexual individuals: multicentre study in four European countries. *Brittish Journal of Psychiatry, 204*(2), 151-156. doi:10.1192/bjp.bp.112.121954

Heylens, G., Verroken, C., De Cock, S., T'Sjoen, G., & De Cuypere, G. (2014b). Effects of different steps in gender reassignment therapy on psychopathology: a prospective study of persons with a gender identity disorder. *Journal of Sexual Medicine, 11*(1), 119-126. doi:10.1111/jsm.12363

Hines, M. (2011). Gender development and the human brain. *Annual Review of Neuroscience, 34*, 69-88. doi:10.1146/annurev-neuro-061010-113654

Hirschfeld, M. (1923). Die Intersexuelle Konstitution. *Jahrbuch fur Sexeulle Zwichenstufen, 27*, 3-27.

Hoenig, J., & Kenna, J. C. (1974). The prevalence of transsexualism in England and Wales. *British Journal of Psychiatry, 124*(579), 181-190.

Hoshiai, M., Matsumoto, Y., Sato, T., Ohnishi, M., Okabe, N., Kishimoto, Y., . . . Kuroda, S. (2010). Psychiatric comorbidity among patients with gender identity disorder. *Psychiatry and Clinical Neurosciences, 64*(5), 514-519. doi:10.1111/j.1440-1819.2010.02118.x

Hovens, J. G . F. M., Wiersma, J. E., Giltay, E. J., Van Oppen, P., Spinhoven, P., Penninx, B.W. J. H., & Zitman, F. G. (2010). Childhood life events and childhood trauma in adult patients with depressive, anxiety and comorbid disorders vs. controls. *Acta Psychiatrica Scandinavica, 122*(1), 66-74. doi:10.1111/j.1600-0447.2009.01491.x

Huelke, D. H. (1949). Ein Transvestit. *Kriminalistik* (3), 91-91.

Huston, A.C. (1983). *Handbook of Child Psychology* (4th ed. Vol. 4). New York: Wiley.

Hwu, H. G., Yeh, E. K., & Chang, L. Y. (1989). Prevalence of psychiatric disorders in Taiwan defined by the Chinese Diagnostic Interview Schedule. *Acta Psychiatrica Scandinavica, 79*(2), 136-147. doi:10.1111/j.1600-0447.1989.tb08581.x

ILGA-Europe, the European Region of the International Lesbian, Gay, Bisexual, Trans and Intersex Association. (2013). The Rainbow Map and Index. Retrieved from https://rainbow-europe.org/

Johansson, A., Sundbom, E., Höjerback, T., & Bodlund, O. (2010). A five-year follow-up study of Swedish adults with gender identity disorder. *Archives of Sexual Behavior, 39*(6), 1429-1437. doi:10.1007/s10508-009-9551-1

Jokinen, Jussi. (2015). Early antecedents of suicide: the role of prenatal and childhood risk factors. *Evidence Based Mental Health, 18*(1), 11. doi:10.1136/eb-2014-101930

Judge, C., O'Donovan, C., Callaghan, G., Gaoatswe, G., & O'Shea, D. (2014). Gender Dysphoria – Prevalence and Co-Morbidities in an Irish Adult Population. *Frontiers in Endocrinology, 5*(87). doi:10.3389/fendo.2014.00087

Junger, J., Pauly, K., Brohr, S., Birkholz, P., Neuschaefer-Rube, C., Kohler, C., . . . Habel, U. (2013). Sex matters: Neural correlates of voice gender perception. *Neuroimage, 79*, 275-287. doi:10.1016/j.neuroimage.2013.04.105

Junger, J., Habel, U., Brohr, S., Neulen, J., Neuschaefer-Rube, C., Birkholz, P., . . . Pauly, K. (2014). More than just two sexes: the neural correlates of voice gender perception in gender dysphoria. *PloS One, 9*(11), e111672. doi:10.1371/journal.pone.0111672

Karlson, P., & Luscher, M. (1959). 'Pheromones': a new term for a class of biologically active substances. *Nature, 183*(4653), 55-56.

Kersting, A., Reutemann, M., Gast, U., Ohrmann, P., Suslow, T., Michael, N., & Arolt, V. (2003). Dissociative disorders and traumatic childhood experiences in transsexuals. *Journal of Nervous and Mental Disease, 191*(3), 182-189.

Kessler, R. C., Adler, L. A., Gruber, M. J., Sarawate, C. A., Spencer, T., & Van Brunt, D. L. (2007). Validity of the World Health Organization Adult ADHD Self-Report Scale (ASRS) Screener in a representative sample of health plan members. *International Journal of Methods in Psychiatric Research, 16*(2), 52-65. doi:10.1002/mpr.208

Kessler, R. C., McLaughlin, K. A., Green, J. G., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., . . . Williams, D. R. (2010). Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. *British Journal of Psychiatry, 197*(5), 378-385. doi:10.1192/bjp.bp.110.080499

Kim, T. S., Cheon, Y. H., Pae, C. U., Kim, J. J., Lee, C. U., Lee, S. J., . . . Lee, C. (2006). Psychological burdens are associated with young male transsexuals in Korea. *Psychiatry and Clinical Neurosciences, 60*(4), 417-421. doi:10.1111/j.1440-1819.2006.01525.x

Kinsey, A.C.P., & Martin, C.E. (1948). *Sexual behavior in the human male.* Philadelphia: Saunders.

Kohlberg, L.A. (1966). *A cognitive-developmental analysis of children's sex role concepts and attitudes* (E.E. Maccoby Ed.). Stanford, California: Stanford University Press.

Kranz, G. S., Hahn, A., Kaufmann, U., Kublbock, M., Hummer, A., Ganger, S., . . . Lanzenberger, R. (2014). White matter microstructure in transsexuals and controls investigated by diffusion tensor imaging. *Journal of Neuroscience, 34*(46), 15466-15475. doi:10.1523/jneurosci.2488-14.2014

Kreukels, B. P., Haraldsen, I. R., De Cuypere, G., Richter-Appelt, H., Gijs, L., & Cohen-Kettenis, P. T. (2012). A European network for the investigation of gender incongruence: the ENIGI initiative. *European Psychiatry, 27*(6), 445-450. doi:10.1016/j.eurpsy.2010.04.009

Kruijver, F. P., Zhou, J. N., Pool, C. W., Hofman, M. A., Gooren, L. J., & Swaab, D. F. (2000). Male-to-female transsexuals have female neuron numbers in a limbic nucleus. *Journal of Clinical Endocrinology and Metabolism, 85*(5), 2034-2041.

Kubie, L. S., & Mackie, J. B. (1968). Critical issues raised by operations for gender transmutation. *Journal of Nervous and Mental Disease, 147*(5), 431-443.

Kulic, D. (1998). *Travesti, Sex, Gender and Culture Among Brazilian Transgendered Prostitutes*. Chicago: University of Chicago Press.

Kuyper, L., & Wijsen, C. (2013). Gender Identities and Gender Dysphoria in the Netherlands. *Archives of Sexual Behavior, 43*(2), 377-385. doi:10.1007/s10508-013-0140-y

Landén, M., Wålinder, J., & Lundström, B. (1996). Prevalence, incidence and sex ratio of transsexualism. *Acta Psychiatrica Scandinavica, 93*(4), 221-223.

Landén, M., & Rasmussen, P. (1997). Gender identity disorder in a girl with autism--a case report. *European Child and Adolescent Psychiatry, 6*(3), 170-173.

Landén, M., Wålinder, J., & Lundström, B. (1998a). Clinical characteristics of a total cohort of female and male applicants for sex reassignment: a descriptive study. *Acta Psychiatrica Scandinavica, 97*(3), 189-194.

Landén, M., Wålinder, J., Hambert, G., & Lundström, B. (1998b). Factors predictive of regret in sex reassignment. *Acta Psychiatrica Scandinavica, 97*(4), 284-289. doi:10.1111/j.1600-0447.1998.tb10001.x

Landén, M. (1999). *Transsexualism, phenomenology, regret after surgery, aetiology, and public attitudes.* (Doctoral), University of Gothenburg, Gothenburg.

Landén, M., & Innala, S. (2000). Attitudes toward transsexualism in a Swedish national survey. *Archives of Sexual Behavior, 29*(4), 375-388.

Lawrence, A. A. (2003). Factors associated with satisfaction or regret following male-to-female sex reassignment surgery. *Archives of Sexual Behavior, 32*(4), 299-315.

Lawrence, A. A. (2010). Sexual orientation versus age of onset as bases for typologies (subtypes) for gender identity disorder in adolescents and adults. *Archives of Sexual Behavior, 39*(2), 514-545. doi:10.1007/s10508-009-9594-3

Lawrence, A.A. (2011). Autogynephilia: an underappreciated paraphilia. *Advances in Psychosomatic Medicine*(31), 135-148. doi:10.1159/000328921

Levine, S. B., & Lothstein, L. (1981). Transsexualism or the gender dysphoria syndromes. *Journal of Sex and Marital Therapy, 7*(2), 85-113. doi:10.1080/00926238108406096

Levine, S. B. (2016). Reflections on the Legal Battles Over Prisoners with Gender Dysphoria. *Journal of the American Academy of Psychiatry and the Law, 44*(2), 236-245.

Lin, C. S., Ku, H. L., Chao, H. T., Tu, P. C., Li, C. T., Cheng, C. M., . . . Hsieh, J. C. (2014). Neural network of body representation differs between transsexuals and cissexuals. *PloS One, 9*(1), e85914. doi:10.1371/journal.pone.0085914

Lindemalm, G., Korlin, D., & Uddenberg, N. (1986). Long-term follow-up of "sex change" in 13 male-to-female transsexuals. *Archives of Sexual Behavior, 15*(3), 187-210.

Lindemalm, G., Körlin, D., & Uddenberg, N. (1987). Prognostic factors vs. outcome in male-to-female transsexualism. *Acta Psychiatrica Scandinavica, 75*(3), 268-274. doi:10.1111/j.1600-0447.1987.tb02788.x

Lombardi, E. L., Wilchins, R. A., Priesing, D., & Diana Malouf, D. . (2002). Gender Violence. *Journal of Homosexuality, 42*(1), 89-101.

Lothstein, L. M. (1979). The Aging Gender Dysphoria (Transsexual) Patient. *Archives of Sexual Behavior, 8*(5), 431-444.

Lothstein, L. M., & Levine, S. B. (1981). Expressive psychotherapy with gender dysphoric patients. *Archives of General Psychiatry, 38*(8), 924-929.

Lundgren, T. K., Isung, J., Rinder, J., Dhejne, C., Arver, S., Holm, L. E., & Farnebo, F. (2016). Moving Transgender Care Forward within Public Health Organizations: Inclusion of Facial Feminizing Surgery in the Swedish National Treatment Recommendations. *Archives of Sexual Behavior, 45*(8), 1879-1880. doi:10.1007/s10508-016-0830-3

Lundström, B. (1981). *Gender dysphoria. A social-psychiatric follow-up of 31 cases not accepted for sex reassignment.* (Doctoral), University of Gothenburg, Gothenburg.

Lundström, B., Pauly, I., & Wålinder, J. (1984). Outcome of sex reassignment surgery. *Acta Psychiatrica Scandinavica, 70*(4), 289-294. doi:10.1111/j.1600-0447.1984.tb01211.x

Lundström, B., & Wålinder, J. (1985). Evaluation of candidates for sex reassignment. *Nordisk Psykiatrisk Tidsskrift, 39*(3), 225-228. doi:10.3109/08039488509106160

Lüders, E., Steinmetz, H., & Jäncke, L. (2002). Brain size and grey matter volume in the healthy human brain. *Neuroreport, 13*(17), Neuroreport.

Madeddu, F., Prunas, A., & Hartmann, D. (2009). Prevalence of Axis II disorders in a sample of clients undertaking psychiatric evaluation for sex reassignment surgery. *Psychiatric Quarterly, 80*(4), 261-267. doi:10.1007/s11126-009-9114-6

Manieri, C., Castellano, E., Crespi, C., Di Bisceglie, C., Dell'Aquila, C., Gualerzi, A., & Molo, M. (2014). Medical treatment of subjects with gender identity disorder: The experience in an Italian public health center. *International Journal of Transgenderism, 15*(2), 53-65.

Manzouri, A., Kosidou, K., & Savic, I. (2015). Anatomical and Functional Findings in Female-to-Male Transsexuals: Testing a New Hypothesis. *Cerebral Cortex.* doi:10.1093/cercor/bhv278

Marantz, S., & Coates, S. (1991). Mothers of boys with gender identity disorder: a comparison of matched controls. *Journal of the American Academy of Child and Adolescent Psychiatry, 30*(2), 310-315.

Marazziti, D., Torri, P., Baroni, S., Catena Dell'Osso, M., Consoli, G., & Boncinelli, V. (2011). Is androstadienone a putative human pheromone? *Current Medicinal Chemistry, 18*(8), 1213-1219.

Marshall, E., Claes, L., Bouman, W. P., Witcomb, G. L., & Arcelus, J. (2016). Non-suicidal self-injury and suicidality in trans people: A systematic review of the literature. *International Review of Psychiatry, 28*(1), 58-69. doi:10.3109/09540261.2015.1073143

Mate-Kole, C, Freschi, M, & Robin, A. (1990). A controlled study of psychological and social change after surgical gender reassignment in selected male transsexuals. *The British Journal of Psychiatry, 157*(2), 261-264. doi:10.1192/bjp.157.2.261

Mazaheri Meybodi, A., Hajebi, A., & Ghanbari Jolfaei, A. (2014a). Psychiatric Axis I Comorbidities among Patients with Gender Dysphoria. *Psychiatry J, 2014*, 971814. doi:10.1155/2014/971814

Mazaheri Meybodi, A., Hajebi, A., & Ghanbari Jolfaei, A. (2014b). The frequency of personality disorders in patients with gender identity disorder. *Medical Journal of the Islamic Republic of Iran*(28), 90.

Meijer, J. H., Eeckhout, G. M., van Vlerken, R. H., & de Vries, A. L. (2017). Gender Dysphoria and Co-Existing Psychosis: Review and Four Case Examples of Successful Gender Affirmative Treatment. *LGBT Health*. doi:10.1089/lgbt.2016.0133

Meyer-Bahlburg, H. F. (2010). From mental disorder to iatrogenic hypogonadism: dilemmas in conceptualizing gender identity variants as psychiatric conditions. *Archives of Sexual Behavior, 39*(2), 461-476. doi:10.1007/s10508-009-9532-4

Meyer, I. H. (2003). Prejudice, social stress, and mental health in lesbian, gay, and bisexual populations: conceptual issues and research evidence. *Psychological Bulletin, 129*(5), 674-697. doi:10.1037/0033-2909.129.5.674

Meyer, J. K. (1982). The Theory of Gender Identity Disorders. *Journal of the American Psychoanalytic Association, 30*(2), 381-418. doi:10.1177/000306518203000204

Meyer zu Hoberge, S. (2009). *Prevalence, incidence and sex ratio of transsexualism in Germany established by counting applications of the German Transsexuals' Act during the period 1991 until 2000.* (Doctoral dissertation), Christian-Albrechts-Universität zu Kiel, Kiel, Germany. http://eldiss.uni-kiel.de/macau/receive/dissertation_diss_00004825 (English abstract) http://d-nb.info/1019984406/34 (German full text) database.

Money, J. (1955). Hermaphroditism, gender and precocity in hyperadrenocorticism: Psychological findings. *Bulletin of the Johns Hopkins Hospital, 96,* 253-264.

Money, J., Hampson, J. G., & Hampson, J. L. (1957). Imprinting and the establishment of gender role. *A.M.A. Archives of Neurology and Psychiatry, 77*(3), 333-336.

Money, John. (1975). Ablatio penis: Normal male infant sex-reassigned as a girl. *Archives of Sexual Behavior, 4*(1), 65-71. doi:10.1007/bf01541887

Money, J. (1994). The Concept of gender identity disorder in childhood and adolescence after 39 years. *Journal of Sex and Marital Therapy, 20*(3), 163-177. doi:10.1080/00926239408403428

Murad, M. H., Elamin, M. B., Garcia, M. Z., Mullan, R. J., Murad, A., Erwin, P. J., & Montori, V. M. (2010). Hormonal therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes. *Clinical Endocrinology, 72*(2), 214-231. doi:10.1111/j.1365-2265.2009.03625.x

Murray, S.O (2000). *Homosexualities*. Chicago: University of Chicago Press.

National Board of Health and Welfare. (2015). *Good care of adults with gender dysphoria, national guidelines (Nationellt kunskapsstöd för vård och behandling av personer med könsdysfori*) Retrieved from http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/19798/2015-4-7.pdf database

Nieder, T. O., Herff, M., Cerwenka, S., Preuss, W. F., Cohen-Kettenis, P. T., De Cuypere, G., . . . Richter-Appelt, H. (2011). Age of onset and sexual orientation in transsexual males and females. *Journal of Sexual Medicine, 8*(3), 783-791. doi:10.1111/j.1743-6109.2010.02142.x

Nieder, T.O., Elaut, E., Richards, C., & Dekker, A. (2016). Sexual orientation of trans adults is not linked to outcome of transition-related health care, but worth asking. *International Review of Psychiatry, 28*(1), 103-111. doi:10.3109/09540261.2015.1102127

Nock, M. K., Borges, G., Bromet, E. J., Alonso, J., Angermeyer, M., Beautrais, A., . . . Williams, D. (2008). Cross-national prevalence and risk factors for suicidal ideation, plans and attempts. *British Journal of Psychiatry, 192*(2), 98-105. doi:10.1192/bjp.bp.107.040113

Nordberg, J. (2015). *The Underground Girls of Kabul: In Search of a Hidden Resistance in Afghanistan*. New York: Broadway Books.

Nuttbrock, L., Bockting, W., Rosenblum, A., Mason, M., Macri, M., & Becker, J. (2012). Gender Identity Conflict/Affirmation and Major Depression Across the Life Course of Transgender Women. *International Journal of Transgenderism, 13*(3), 91-103. doi:10.1080/15532739.2011.657979

Nuttbrock, L., Bockting, W., Rosenblum, A., Hwahng, S., Mason, M., Macri, M., & Becker, J. (2014). Gender abuse and major depression among transgender women: a prospective study of vulnerability and resilience. *American Journal of Public Health, 104*(11), 2191-2198. doi:10.2105/AJPH.2013.301545

Nygren, U., Nordenskjöld, A., Arver, S., & Södersten, M. (2016). Effects on Voice Fundamental Frequency and Satisfaction with Voice in Trans Men during Testosterone Treatment-A Longitudinal Study. *Journal of Voice, 30*(6), 766.e723-766.e734. doi:10.1016/j.jvoice.2015.10.016

O'Gorman, E. C. (1982). A retrospective study of epidemiological and clinical aspects of 28 transsexual patients. *Archives of Sexual Behavior, 11*(3), 231-236.

Olsson, S. E., & Möller, A. R. (2003). On the incidence and sex ratio of transsexualism in Sweden, 1972-2002. *Archives of Sexual Behavior, 32*(4), 381-386.

Olsson, S. E., & Möller, A. (2006). Regret after sex reassignment surgery in a male-to-female transsexual: a long-term follow-up. *Archives of Sexual Behavior, 35*(4), 501-506. doi:10.1007/s10508-006-9040-8

Parker, G., & Barr, R. (1982). Parental representations of transsexuals. *Archives of Sexual Behavior, 11*(3), 221-230. doi:10.1007/bf01544990

Pauly, I.B. (1968). The current status of the change of sex operation. *The journal of nervous and mental disease, 147*(5), 460-471.

Person, E., & Ovesey, L. (1974a). The transsexual syndrome in males. I. Primary transsexualism. *American Journal of Psychotherapy, 28*(1), 4-20.

Person, E., & Ovesey, L. (1974b). The transsexual syndrome in males. II. Secondary transsexualism. *American Journal of Psychotherapy, 28*(2), 174-193.

Pfäfflin, F., & Junge, A. (1992). *Geschlechtsumwandlung. Abhandlungen zur transsexualitaet [Sex Reassignment: Treatments for Transsexualism]*.

Pfäfflin, F. (2011). Remarks on the history of the terms identity and gender identity. *International Journal of Transgenderism, 13*(1), 13-25.

Pimenoff, V. (2006). On the care of transsexuals in Finland. *International Journal of Transgenderism, 9*, 23-33.

Pimenoff, V., & Pfäfflin, F. (2011). Transsexualism: Treatment Outcome of Compliant and Noncompliant Patients. *International Journal of Transgenderism, 13*(1), 37-44. doi:10.1080/15532739.2011.618399

Poasa, K. H., Blanchard, R., & Zucker, K. J. (2004). Birth order in transgendered males from Polynesia: a quantitative study of Samoan fa'afafine. *Journal of Sex and Marital Therapy, 30*(1), 13-23. doi:10.1080/00926230490247110

Prunas, A., Bandini, E., Fisher, A. D., Maggi, M., Pace, V., Quagliarella, L., . . . Bini, M. (2016). Experiences of Discrimination, Harassment, and Violence in a Sample of Italian Transsexuals Who Have Undergone Sex-Reassignment Surgery. *J Interpers Violence*. doi:10.1177/0886260515624233

Public Health Agency of Sweden. (2015). Health and health determinants among transgender persons – a report on the health status of transgender persons in Sweden. Retrieved from http://www.folkhalsomyndigheten.se/pagefiles/20250/halsan-halsans-bestamningsfaktorer-transpersoner-15038-webb.pdf website:

Rametti, G., Carrillo, B., Gomez-Gil, E., Junque, C., Segovia, S., Gomez, A., & Guillamon, A. (2011a). White matter microstructure in female to male transsexuals before cross-sex hormonal treatment. A diffusion tensor imaging study. *Journal of Psychiatric Research, 45*(2), 199-204. doi:10.1016/j.jpsychires.2010.05.006

Rametti, G., Carrillo, B., Gomez-Gil, E., Junque, C., Zubiarre-Elorza, L., Segovia, S., . . . Guillamon, A. (2011b). The microstructure of white matter in male to female transsexuals before cross-sex hormonal treatment. A DTI study. *Journal of Psychiatric Research, 45*(7), 949-954. doi:10.1016/j.jpsychires.2010.11.007

Rasmussen, K. (1930). *Iglulik and Caribou Eskimos Reports from the 5th Thule Expedition 1921-24*. Copenhagen.

Reed, G. M., Drescher, J., Krueger, R. B., Atalla, E., Cochran, S. D., First, M. B., . . . Saxena, S. (2016). Disorders related to sexuality and gender identity in the ICD-11: revising the ICD-10 classification based on current scientific evidence, best clinical practices, and human rights considerations. *World Psychiatry, 15*(3), 205-221. doi:10.1002/wps.20354

Reisner, S. L., Deutsch, M. B., Bhasin, S., Bockting, W., Brown, G. R., Feldman, J., . . . Goodman, M. (2016a). Advancing methods for US transgender health research. *Current Opinion in Endocrinology, Diabetes, and Obesity, 23*(2), 198-207. doi:10.1097/med.0000000000000229

Reisner, S. L., Poteat, T., Keatley, J., Cabral, M., Mothopeng, T., Dunham, E., . . . Baral, S. D. (2016b). Global health burden and needs of transgender populations: a review. *Lancet, 388*(10042), 412-436. doi:10.1016/s0140-6736(16)00684-x

Reisner, S. L., White Hughto, J. M., Gamarel, K. E., Keuroghlian, A. S., Mizock, L., & Pachankis, J. E. (2016c). Discriminatory experiences associated with posttraumatic stress disorder symptoms among transgender adults. *Journal of Counseling Psychology, 63*(5), 509-519. doi:10.1037/cou0000143

Rekers, George A., Mead, Shasta L., Rosen, Alexander C., & Brigham, Steven L. (1983). Family Correlates of Male Childhood Gender Disturbance. *The Journal of Genetic Psychology, 142*(1), 31-42. doi:10.1080/00221325.1983.10533493

Richards, C., Bouman, W.P., Seal, L., Barker, M.J., Nieder, T.O., & T'Sjoen, G. (2016). Non-binary or genderqueer genders. *International Review of Psychiatry, 28*(1), 95-102. doi:10.3109/09540261.2015.1106446

Ross, M. W., Walinder, J., Lundstrom, B., & Thuwe, I. (1981). Cross-cultural approaches to transsexualism. A comparison between Sweden and Australia. *Acta Psychiatrica Scandinavica, 63*(1), 75-82.

Ross, M. W., & Need, J. A. (1989). Effects of adequacy of gender reassignment surgery on psychological adjustment: a follow-up of fourteen male-to-female patients. *Archives of Sexual Behavior, 18*(2), 145-153.

Rothman, J. R. (2002). *Epidemiology an Introduction*. Oxford: Oxford University Press.

Ruigrok, A. N. V., Salimi-Khorshidi, G., Lai, M-C, Baron-Cohen, S., Lombardo, M. V., Tait, R. J., & Suckling, J. (2014). A meta-analysis of sex differences in human brain structure. *Neuroscience and Biobehavioral Reviews, 39*, 34-50. doi:http://dx.doi.org/10.1016/j.neubiorev.2013.12.004

Ruppin, U., & Pfäfflin, F. (2015). Long-Term Follow-Up of Adults with Gender Identity Disorder. *Archives of Sexual Behavior*. doi:10.1007/s10508-014-0453-5

Rushton, J. P., & Ankney, C. D. (2009). Whole Brain Size and General Mental Ability: A Review. *International Journal of Neuroscience, 119*(5), 692-732. doi:10.1080/00207450802325843

Safer, J. D., & Pearce, E. N. (2013). A simple curriculum content change increased medical student comfort with transgender medicine. *Endocrine Practice, 19*(4), 633-637. doi:10.4158/ep13014.or

Safer, J. D. (2016). The large gaps in transgender medical knowledge among providers must be measured and addressed. *Endocrine Practice, 22*(7), 902-903. doi:10.4158/ep161388.co

Savic, I., Berglund, H., Gulyas, B., & Roland, P. (2001). Smelling of odorous sex hormone-like compounds causes sex-differentiated hypothalamic activations in humans. *Neuron, 31*(4), 661-668.

Savic, I., Berglund, H., & Lindström, P. (2005). Brain response to putative pheromones in homosexual men. *Proceedings of the National Academy of Sciences of the United States of America, 102*(20), 7356-7361. doi:0407998102 [pii]10.1073/pnas.0407998102

Savic, I., Garcia-Falgueras, A., & Swaab, D. F. (2010). Sexual differentiation of the human brain in relation to gender identity and sexual orientation. *Progress in Brain Research, 186*, 41-62. doi:10.1016/b978-0-444-53630-3.00004-x

Savic, I., & Arver, S. (2011). Sex dimorphism of the brain in male-to-female transsexuals. *Cerebral Cortex, 21*(11), 2525-2533. doi:10.1093/cercor/bhr032 bhr032 [pii]

Schaltenbrand, G., & Bailey, P. (1959). *Introduction to stereotaxis, with an atlas of the human brain*. Stuttgart: G Tieme.

Selvaggi, G., & Giordano, S. (2014). The role of mental health professionals in gender reassignment surgeries: unjust discrimination or responsible care? *Aesthetic Plastic Surgery, 38*(6), 1177-1183. doi:10.1007/s00266-014-0409-0

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., . . . Dunbar, G. C. (1998). The Mini International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry, 59 Suppl 20*, 22-33;quiz 34-57.

Sigurjonsson, H., Rinder, J., Möllermark, C., Farnebo, F., & Lundgren, T. K. (2015). Male to female gender reassignment surgery: Surgical outcomes of consecutive patients during 14 years. *JPRAS Open, 6*, 69-73. doi:http://dx.doi.org/10.1016/j.jpra.2015.09.003

Simon, L., Zsolt, U., Fogd, D., & Czobor, P. (2011). Dysfunctional core beliefs, perceived parenting behavior and psychopathology in gender identity disorder: A comparison of male-to-female, female-to-male transsexual and nontranssexual control subjects. *Journal of Behavior Therapy and Experimental Psychiatry, 42*(1), 38-45. doi:http://dx.doi.org/10.1016/j.jbtep.2010.08.004

Simonsen, R. K., Giraldi, A., Kristensen, E., & Hald, G. M. (2016a). Long-term follow-up of individuals undergoing sex reassignment surgery: Psychiatric morbidity and mortality. *Nordic Journal of Psychiatry, 70*(4), 241-247. doi:10.3109/08039488.2015.1081405

Simonsen, R. K., Hald, G. M., Kristensen, E., & Giraldi, A. (2016b). Long-Term Follow-Up of Individuals Undergoing Sex-Reassignment Surgery: Somatic Morbidity and Cause of Death. *Sex Med, 4*(1), e60-e68. doi:http://dx.doi.org/10.1016/j.esxm.2016.01.001

Skagerberg, E. , Parkinson, R., & Carmichael, P. (2013). Selfharming thoughts and behaviors in a group of children and adolescents with gender dysphoria. *International Journal of Transgenderism, 14*, 86-92.

Smith, E. S., Junger, J., Derntl, B., & Habel, U. (2015). The transsexual brain--A review of findings on the neural basis of transsexualism. *Neuroscience and Biobehavioral Reviews, 59*, 251-266. doi:10.1016/j.neubiorev.2015.09.008

Smith, Y. L., van Goozen, S. H., Kuiper, A. J., & Cohen-Kettenis, P. T. (2005). Transsexual subtypes: clinical and theoretical significance. *Psychiatry Research, 137*(3), 151-160. doi:S0165-1781(05)00155-1 [pii]10.1016/j.psychres.2005.01.008

Socarides, C. W. (1970). A psychoanalytic study of the desire for sexual transformation (transsexualism): The plaster-of-Paris man. *International Journal of Psychoanalysis, 51*, 341-349.

Steensma, T. D., Kreukels, B. P. C., de Vries, A. L. C., & Cohen-Kettenis, P. T. (2013). Gender identity development in adolescence. *Hormones and Behavior, 64*(2), 288-297. doi:http://dx.doi.org/10.1016/j.yhbeh.2013.02.020

Stefánsson, J. G., Líndal, E., Björnsson, J. K., & Guðomundsdóttir, Á. (1991). Lifetime prevalence of specific mental disorders among people born in Iceland in 1931. *Acta Psychiatrica Scandinavica, 84*(2), 142-149. doi:10.1111/j.1600-0447.1991.tb03118.x

Stoller, R.J. (1968). *Sex and Gender, Vol.1: On the development of masculinity and femininity*. New York: Science House.

Stoller, R. J. (1976). Two feminized male American Indians. *Archives of Sexual Behavior, 5*(6), 529-538.

Stryker, S. (2008). *Transgender history*. Berkley: Seal Press.

Statistics Sweden. (2012). Retrieved from http://www.scb.se/Pages/SSD/SSD_SelectVariables____340507.aspx?px_tableid=ssd_extern%3aBefolkningNy&rxid=0b3f5d00-ca4f-4813-9c77-5803f5fff6da

Söderpalm, E. (1996). *Transsexualism i ett logopediskt perspektiv.* Lund, Sweden: Studentlitteratur.

Söderpalm, E., Larsson, A., & Almquist, S. A. (2004). Evaluation of a consecutive group of transsexual individuals referred for vocal intervention in the west of Sweden. *Logoped Phoniatr Vocol, 29*(1), 18-30.

Sørensen, T., & Hertoft, P. (1980). Sexmodifying operations on transsexuals in Denmark in the period 1950–1977. *Acta Psychiatrica Scandinavica, 61*(1), 56-66. doi:10.1111/j.1600-0447.1980.tb00565.x

Sørensen, T. (1981). A follow-up study of operated transsexual males. *Acta Psychiatrica Scandinavica, 63*(5), 486-503. doi:10.1111/j.1600-0447.1981.tb00698.x

Sørensen, T., & Hertoft, P. (1982). Male and female transsexualism: The Danish experience with 37 patients. *Archives of Sexual Behavior, 11*(2), 133-155. doi:10.1007/bf01541980

Talairach, J., & Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain: 3-dimensional proportional system: an approach to medical cerebral imaging*. New York: Tieme.

Transgender Europe. (2017). Transgender murder monitoring. http://transrespect.org/en/research/trans-murder-monitoring/), from Transgender Europe

Tsoi, W. F., Kok, L. P., & Long, F. Y. (1977). Male transsexualism in Singapore: a description of 56 cases. *British Journal of Psychiatry, 131*, 405-409.

Tsoi, W. F. (1988). The prevalence of transsexualism in Singapore. *Acta Psychiatrica Scandinavica, 78*(4), 501-504.

Udeze, B., Abdelmawla, N., Khoosal, D. , & Terry, T. (2008). Psychological functions in male-to-female transsexual people before and after surgery. *Sexual and Relationship Therapy, 23*(2), 141-145. doi:10.1080/14681990701882077

Ujike, H., Otani, K., Nakatsuka, M., Ishii, K., Sasaki, A., Oishi, T., . . . Kuroda, S. (2009). Association study of gender identity disorder and sex hormone-related genes. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 33*(7), 1241-1244. doi:10.1016/j.pnpbp.2009.07.008

Wallien, M. S., van Goozen, S. H., & Cohen-Kettenis, P. T. (2007). Physiological correlates of anxiety in children with gender identity disorder. *European Child and Adolescent Psychiatry, 16*(5), 309-315. doi:10.1007/s00787-007-0602-7

Wallien, M.S.C. (2008). *Gender identity dysphoria in childhood: causes and consequences.* (Doctoral dissertation), VU University medical center Amsterdam.

Van Der Miesen, A. I., Hurley, H., & De Vries, A. L. (2016). Gender dysphoria and autism spectrum disorder: A narrative review. *International Review of Psychiatry, 28*(1), 70-80. doi:10.3109/09540261.2015.1111199

van Kesteren, P. J., Gooren, L. J., & Megens, J. A. (1996). An epidemiological and demographic study of transsexuals in The Netherlands. *Archives of Sexual Behavior, 25*(6), 589-600.

van Kesteren, P. J., Asscheman, H., Megens, J. A., & Gooren, L. J. (1997). Mortality and morbidity in transsexual subjects treated with cross-sex hormones. *Clinical Endocrinology, 47*(3), 337-342.

Vancouver Costal Health, Provincial Health Services Authority. (2016). Transgender Health Information Program, Glossary. Retrieved from http://transhealth.phsa.ca/trans-101/glossary

VanderLaan, D.P., & Vasey, P.L. (2011). Male Sexual Orientation in Independent Samoa: Evidence for Fraternal Birth Order and Maternal Fecundity Effects. *Archives of Sexual Behavior, 40*(3), 495-503. doi:10.1007/s10508-009-9576-5

Veale, J. F. (2008). Prevalence of transsexualism among New Zealand passport holders. *Australian and New Zealand Journal of Psychiatry, 42*(10), 887-889. doi:902174341 [pii]10.1080/00048670802345490

Weinand, J. D., & Safer, J. D. (2015). Hormone therapy in transgender adults is safe with provider supervision; A review of hormone therapy sequelae for transgender individuals. *J Clin Transl Endocrinol, 2*(2), 55-60. doi:10.1016/j.jcte.2015.02.003

Weitze, C., & Osburg, S. (1996). Transsexualism in Germany: empirical data on epidemiology and application of the German Transsexuals' Act during its first ten years. *Archives of Sexual Behavior, 25*(4), 409-425.

Wierckx, K., Elaut, E., Van Hoorde, B., Heylens, G., De Cuypere, G., Monstrey, S., . . . T'Sjoen, G. (2014). Sexual desire in trans persons: associations with sex reassignment treatment. *Journal of Sexual Medicine, 11*(1), 107-118. doi:10.1111/jsm.12365

Wilson, P., Sharp, C., & Carr, S. (1999). The prevalence of gender dysphoria in Scotland: a primary care study. *British Journal of General Practice, 49*(449), 991-992.

Winter, S. (2009). Cultural Considerations for the World Professional Association for Transgender Health's Standards of Care: The Asian Perspective. *International Journal of Transgenderism, 11*(1), 19-41. doi:10.1080/15532730902799938

Winter, S., Diamond, M., Green, J., Karasic, D., Reed, T., Whittle, S., & Wylie, K. (2016). Transgender people: health at the margins of society. *Lancet, 388*(10042), 390-400. doi:10.1016/s0140-6736(16)00683-8

Vogt, J. H. (1968). Five cases of transsexualism in females. *Acta Psychiatrica Scandinavica, 44*(1), 62-88. doi:10.1111/j.1600-0447.1968.tb07636.x

von Vogelsang, A-C., Milton, C., Ericsson, I., & Strömberg, L. (2016). 'Wouldn't it be easier if you continued to be a guy?' – a qualitative interview study of transsexual persons' experiences of encounters with healthcare professionals. *Journal of Clinical Nursing*, n/a-n/a. doi:10.1111/jocn.13271

Woodbury-Smith, R. M., Robinson, J., Wheelwright, S., & Baron-Cohen, S. (2005). Screening Adults for Asperger Syndrome Using the AQ:A Preliminary Study of its Diagnostic Validity in Clinical Practice. *Journal of Autism and Developmental Disorders, 35*(3), 331-335. doi:10.1007/s10803-005-3300-7

World Health Organization. (1967). *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death, Eighth Revision*: Author.

World Health Organization. (1978). *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death, Ninth Revision* Geneva: Author.

World Health Organization. (1992). *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death, Tenth Revision*. Geneva: Author.

Vujovic, S., Popovic, S., Sbutega-Milosevic, G., Djordjevic, M., & Gooren, L. (2008). Transsexualism in Serbia: A Twenty-Year Follow-Up Study. *Journal of Sexual Medicine*.

Vujovic, S., Popovic, S., Sbutega-Milosevic, G., Djordjevic, M., & Gooren, L. (2009). Transsexualism in Serbia: a twenty-year follow-up study. *Journal of Sexual Medicine, 6*(4), 1018-1023. doi:10.1111/j.1743-6109.2008.00799.x

Wulff, H.R., Andur Pedersen, S., & Rosenberg, R. N. . (1990). *Philosophy of medicine: an introduction*. Oxford: Blackwell Scientific Publications.

Wyatt, T. D. (2015). The search for human pheromones: the lost decades and the necessity of returning to first principles. *Proceedings: Biological Sciences, 282*(1804), 20142994. doi:10.1098/rspb.2014.2994

Wålinder, J. (1967). *Transsexualism: a study of forty-three cases.* (Doctoral), University of Gothenburg, Gothenburg.

Wålinder, J. (1968). Transsexualism: definition, prevalence and sex distribution. *Acta Psychiatrica Scandinavica. Supplementum, 203*, 255-258.

Wålinder, J. (1971). Incidence and sex ratio of transsexualism in Sweden. *British Journal of Psychiatry, 119*(549), 195-196.

Wålinder, J & Thuwe, I.. (1975). *A social-psychiatric follow-up study of 24 sex-reassigned transsexual.* Gothenburg University, Gothenburg.

Wålinder, J., & Thuwe, I. (1976). A law concerning sex reassignment of transsexuals in Sweden. *Archives of Sexual Behavior, 5*(3), 255-258.

Wålinder, J., Lundström, B., & Thuwe, I. (1978). Prognostic factors in the assessment of male transsexuals for sex reassignment. *Brittish journal of psychiatry, 132*, 16-20.

Zeluf, G., Dhejne, C., Orre, C., Nilunger Mannheimer, L., Deogan, C., Höijer, J., & Ekéus Thorson, A. (2016). Health, disability and quality of life among trans people in Sweden–a web-based survey. *BMC Public Health, 16*(1), 1-15. doi:10.1186/s12889-016-3560-5

Zhou, J. N., Hofman, M. A., Gooren, L. J., & Swaab, D. F. (1995). A sex difference in the human brain and its relation to transsexuality. *Nature, 378*(6552), 68-70. doi:10.1038/378068a0

Zubiaurre-Elorza, L., Junque, C., Gomez-Gil, E., Segovia, S., Carrillo, B., Rametti, G., & Guillamon, A. (2013). Cortical thickness in untreated transsexuals. *Cerebral Cortex, 23*(12), 2855-2862. doi:10.1093/cercor/bhs267

Zucker, K. J., & Kuksis, M. (1990). Gender dysphoria and sexual abuse: a case report. *Child Abuse and Neglect, 14*(2), 281-283.

Zucker, K.J., & Bradley, S.J. (1995). *Gender identity disorder and psychosexual problems in children and adolescents*. New York: Guildford Press.

Zucker, K. J., Lightbody, S., Pecore, K., Bradley, S. J., & Blanchard, R. (1998). Birth order in girls with gender identity disorder. *European Child and Adolescent Psychiatry, 7*(1), 30-35.

Zucker, K. J., Blanchard, R., Kim, T. S., Pae, C. U., & Lee, C. (2007). Birth order and sibling sex ratio in homosexual transsexual South Korean men: Effects of the male-preference stopping rule. *Psychiatry and Clinical Neurosciences, 61*(5), 529-533. doi:10.1111/j.1440-1819.2007.01703.x

Zucker, K. J., Lawrence, A. A., & Kreukels, B. P. (2016). Gender Dysphoria in Adults. *Annual Review of Clinical Psychology*. doi:10.1146/annurev-clinpsy-021815-09303

Ösby, U., Brandt, L., Correia, N., Ekbom, A., & Sparen, P. (2001). Excess mortality in bipolar and unipolar disorder in Sweden. *Archives of General Psychiatry, 58*(9), 844-850.

10 APPENDIX

Table 15. Cross-sectional studies (2000-2016) investigating psychiatric morbidity and psychopathology in transgender persons attending transgender health care.

Table 15. Cross-sectional studies (2000-2016) investigating psychiatric morbidity and psychopathology in transgender persons attending transgender health care.

Authors (year) Country	Number of trans participants / mean age at assessment	Diagnosis	Treatment status: (on CHT or post GCGS)	Study design	Comparative groups	Outcome measure	Prevalence of psychiatric morbidity and psychopathology	Subgroup differences /comments
Haraldsen & Dahl (2000) Norway	35 TM 51 TW --- 34.0 y TM 33.3 y TW	DSM-III-R DSM-IV	CHT NR GCGS Mixed pre and post surgery	Single center (Gender Clinic) Cross-sectional	CC 1068 Personality disorder (PD) 101	SCID-I, SCID-II GAF SCL-90-R	Any Axis I diagnosis (mostly depression and anxiety) 33% Any Axis II diagnosis 20% SCL-90-R as per CC	Groups: Trans lower scores in SCL-90-R than PD Gender: TW lower SCL-90-R vs. TM
Miach et al. (2000) Australia	82 TW: 48 GID 34 GIDAANT --- 33.5 y	DSM-III-R	CHT NR GCGS 0%	Single center: (Gender Clinic) Cross-sectional	GID vs. GIDAANT	MMPI-2	Psychopathology: Low in 85% of GID High in 47% of GIDAANT	GID differs significantly in degree of psychopathology from GIDAANT
Kersting et al. (2003) Germany	12 TM 29 TW --- 34.7 y	DSM-IV	CHT NR GCGS 17%	Single center (Gender Clinic) Cross-sectional	Psychiatric inpatients 115 Normative data	DES SCID-D	Dissociative symptoms: Trans similar to psychiatric inpatients	Limitations: DES and SCID-D limited validity in trans people
Hepp et al. (2005) Switzerland	11 TM 20 TW --- 33.2y	DSM-IV	CHT 32% GCGS 23%	Single center (Gender Clinic) Cross-sectional	No	SCID-I, SCID-II HADS	Any Axis I diagnosis, lifetime, (mostly depression and anxiety diagnoses and substance abuse) 71% Any Axis I diagnosis current, (mostly anxiety) 39% Axis II diagnosis 42%	No differences, regarding gender, age, and treatment status
Kim et al. (2006) Korea	43 TW --- 20.4 y	DSM-IV	CHT 88% GCGS 26%	Single center (Identified as part of the military service examination with gender dysphoria) Cross-sectional	Cisgender men 47, matched for age and education	BDI SADS SES	BDI (mean) 21.4 SADS (mean) 13.6 SES (mean) 16.5	Trans significantly higher scores on depression, and social anxiety and lower scores on self-esteem than controls

Authors (year) Country	**Number of trans participants / mean age at assessment**	**Diagnosis**	**Treatment status: (on CHT or post GCGS)**	**Study design**	**Comparative groups**	**Outcome measure**	**Prevalence of psychiatric morbidity and psychopathology**	**Subgroup differences /comments**
Gomez-Gil et al. (2008) Spain[1]	56 TM 107 TW ---------- 27.3 y TM 29.9 y TW	DSM-IV	CHT NR GCGS 0%	Single center (Gender Clinic) Cross-sectional	Normative data	MMPI-2	MMPI-2: Within normal range.	Gender: TW not on CHT scored higher than on CHT. TM no difference regarding CHT status Limitation: Pre-post groups were not the same
Gomez-Gil et al. (2009)[1] Spain	71 TM 159 TW ---------- 27.3 y TM 29.7 y TW	DSM-IV-TR ICD-10	CHT 49% GCGS 0%	Single center (Gender Clinic) Cross-sectional	No	MINI	<u>Any lifetime psychiatric diagnosis:</u> Mood and adjustment diagnoses 71% (TM) and 56% (TW) Non-alcohol substance abuse/dependence 0% (TW) Generalized anxiety disorder 9% (TW) and 6% (TM) <u>Any current psychiatric diagnosis:</u> Social phobia 11% (TM) and 8% (TW)	Adjustment disorders and substance abuse more frequent in TW vs. TM
Madeddu et al. (2009) Italy	16 TM 34 TW ------ 31.7 y	DSM-IV-TR	CHT 36% GCGS 0%	Single center (Gender Clinic) Cross-sectional	No	SCID-II	Axis II diagnosis 52% Most frequent PD Narcissistic	Gender: no Axis II differences
Weyers et al. (2009) Belgium	50 TW ---------- 43.06 y	ICD-10	CHT 100% GCGS 100%	Single center (Gender Clinic) Cross-sectional	Normative data	SF-36	Mental health problems: No difference to normative data	Relationship: less psychopathology if in a relationship
Hoshiai et al. (2010) Japan	349 TM 230 TW ------- 26.5 y TM 32.0 y TW	DSM-IV	CHT 32% GCGS 12%	Single center (Gender Clinic) Cross-sectional	No	Clinical interview and clinical records	Any Axis I diagnosis 14% Adjustment disorder 7%, Anxiety diagnoses 4%, Mood diagnoses 1%	Gender: more Axis I TW vs. TM

Authors (year) Country	Number of trans participants / mean age at assessment	Diagnosis	Treatment status: (on CHT or post GCGS)	Study design	Comparative groups	Outcome measure	Prevalence of psychiatric morbidity and psychopathology	Subgroup differences /comments
Bandini et al. (2011)[2] Italy	109 TW -------- 36.0 y	DSM-IV-TR	CHT 71% GCGS 26%	Single center (Gender Clinic) Cross-sectional	Trans with and without childhood maltreatment (CM)	Psychiatric interview SCL-90-R	Any lifetime psychiatric diagnosis: 67%(CM) /37% (non-CM) SCL-90-R: no difference between groups	CM group higher body dissatisfaction and worse lifetime mental health
Simon et al. (2011) Hungary	17 TM 30 TW -------- 28.0 y TM 26.0 y TW	DSM-IV	CHT NR GCGS 0%	Single center (Gender Clinic) Cross-sectional	CC 157	SCL-90-R	Psychopathology: SCL-90-R: No differences compared to controls	Gender: TW elevated levels of interpersonal sensitivity
Gomez-Gil et al. (2012)[1] Spain	74 TM 113 TW ---------- 29.7 y	ICD-10 DSM-IV-TR	CHT 36% GCGS 42%	Single center (Gender Clinic) Cross-sectional	Trans with and without treatment Normative data	SADS HAD-A HAD-D	Social anxiety, depression and anxiety: SADS, HADS scores normal range except for HAD-A. Differences CHT or not: CHT group lower scores.	Gender: no difference CHT: CHT group better when compared to not treated Limitation: Pre-post groups were not the same
Gorin-Lazard et al. (2012)[3] France	30TM 31 TW ---------- 29.9y TM 39.4y TW	DSM-IV-TR	CHT 72% GCGS NR	Multi-center (Gender Clinics) Cross-sectional	No	BDI	Depression: 25% significant scores in the BDI	Gender: no difference
Auer et al. (2013) Germany	32 TM 57 TW ---------- 32.3 y TM 47.9 y TW	ICD-10	CHT 100% GCGS 65%	Single center (Endocrinology Clinic) Cross-sectional	CC336 matched for age and sex (natal and phenotype)	SCL-90-R	Psychopathology: SCL-90-R worse scores on all scales compared controls	Gender: Depressive symptoms higher in TW TM had a profile as cis males TW were more similar to cis females
Fisher et al. (2013)[2] Italy	48 TM 92 TW ---------- 32.6 y	DSM-IV-TR	CHT 70% GCGS 22%	Single center (Gender Clinic) Cross-sectional	No	SCID-I, SCID-II SCL-90-R	Any Axis I diagnosis 19% Mood and adjustment diagnoses 11% Anxiety diagnoses 5% Any Axis II diagnosis 4%	Gender: no difference

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Gorin-Lazard et al. (2013)[3] France	31TM 36 TW ---------- 35.1 y	DSM-IV-TR	CHT 73% GCGS NR	Multi-center (Gender Clinics) Cross-sectional	Trans with and without CHT	BDI SSEI	Depression and Self-esteem: Trans on CHT less depressive symptoms, better self esteem	CHT: CHT group better vs. not on CHT Limitation: Pre-post groups were not the same
Davey et al. (2014) UK	40 TM 63 TW ---------- 45.7 y	ICD-10	CHT 79% GCGS 17 %	Single center (Gender Clinic) Cross-sectional	CC 103 Controlled by age	SCL-90-R	Psychopathology: SCL-90-R scores higher in trans	Social support did not significantly predict psychopathology
Duisin et al. (2014) Serbia	9 TM 21 TW --------- 30.4 y	DSM-IV-TR	CHT NR GCGS 0%	Single center (Gender Clinic) Cross-sectional	CC 30	SCID-II	Any Axis II diagnosis 67% (most frequent paranoid and avoidant)	Difference: GID group more Axis II diagnosis compared to CC group Gender: TW more psychopathology vs. TM
Fisher et al. (2014)[2] Italy	59 TM 66 TW ------- 28.7 y TM 33.1 y TW	DSM-IV-TR	CHT 0% GCGS NR	Multi-center (Gender Clinics) Cross-sectional	Trans with and without CHT	SCL-90-R BUT GSI	Psychopathology: No difference between CHT group and no CHT group on SCL-90-R. BUT GSI: TW with CHT group had less body uneasiness than not treated group	Body uneasiness effectively diminished with CHT Limitation: Pre-post groups were not the same
Judge et al. (2014) Ireland	59 TM 159 TW ---------- 32.6 y	DSM-IV-TR	CHT 20% GCGS 2%	Single center (Gender Clinic) Cross-sectional	No	Psychiatric assessment by mental health professional	Depression (lifetime) 34% Schizophrenia 4% Bipolar disorder 2%	High prevalence of psychiatric conditions Limitation: no controls
Heylens et al. (2014 a) Belgium Germany The Netherlands Norway	123 TM 182 TW ---------- 22.8-31.2 y TM 21.6-36.5 y TW (Depends on country)	DSM-IV-TR	CHT 0% GCGS 0%	Multi-center (Gender Clinics) 4 countries Cross-sectional	No	MINI SCID-II	Any lifetime Axis I diagnosis 70% Affective problems 60%, Anxiety problems 28% Any current Axis I diagnosis 38% Affective problems 27%, Anxiety problems 17% Axis II diagnosis 15 %	Gender: no differences Age of onset: no differences

Authors (year) Country	Number of trans participants / mean age at assessment	Diagnosis	Treatment status: (on CHT or post GCGS)	Study design	Comparative groups	Outcome measure	Prevalence of psychiatric morbidity and psychopathology	Subgroup differences /comments
Mazaheri Meybodi et al. (2014 a) Iran	36 TM 47 TW ---------- Age: NR	DSM-IV-TR	CHT 93% GCGS 0%	Single center (Gender Clinic) Cross-sectional	No	SCID-I	Axis I diagnosis 63% Major depressive disorder 34% Specific phobia 21% Adjustment disorder 16%	High prevalence of Axis I diagnoses Limitation: no controls
Mazaheri Meybodi et al. (2014 b) Iran	31 TM 39 TW ---------- Age: NR	DSM-IV-TR	CHT 93% GCGS 0%	Single center (Gender Clinic) Cross-sectional	No	MCMI-II	Axis-II diagnosis 81% Narcissistic PD 57%	High prevalence of Axis II diagnoses. Limitation: no controls
Claes et al. (2015) UK	52 TM 103 TW ---------- 34.5 y	ICD-10	CHT 0% GCGS 0%	Single center (Gender Clinic) Cross-sectional	No	SCL-90-R RSE	Psychopathology: TW reported significantly higher scores on paranoid ideation, interpersonal distrust, anxiety, depression and obsessive-compulsive complaints compared with TM	Gender: TW significantly lower level of self-esteem vs. TM
Colizzi et al. (2015) Italy	33 TM 85 TW ----- 30.2 y	DSM-IV-TR	CHT 0% GCGS 0%	Single center (Gender Clinic) Cross-sectional	No	DDIS DES	Dissociative disorders 30%	Gender: No differences
Simonsen et al. (2015)	48 TM 56 TW ----- 32.6 y TM[4], 37.1 y TW[4]	ICD-8, 9 and 10	CHT 100% GCGS 100%	National register Cross-sectional	No	Psychiatric diagnoses in National register	<u>Prior to gender transition</u> Any psychiatric diagnosis 28% <u>After gender transition</u> Any psychiatric diagnosis 22%	Gender: No differences 7% had a psychiatric diagnosis both before and after gender transition
Bergero-Miguel et al. (2016)	101 TM 109 TW ----- 27.9 y	ICD-10	NR	Single center (Gender Clinic) Cross-sectional	No	MINI BDI-II	Social anxiety disorder 31% (36% TM and 28% TW) Mild depression 13% Moderate depression 12% Serious depression 7%	Social anxiety disorder were associated with depression, current use of cannabis, hospitalization of parents during childhood and immigrant status

BDI = Beck Depression Inventory; BUT-GSI = Body Uneasiness Test Global Severity Index (the total score of BUT); CC = Cis controls; CHT = cross-sex hormonal treatment; CM = childhood maltreatment; DES = Dissociative Experience Scale; DDIS = Dissociative Disorders Interview Schedule; GAF = Global Assessment of Functioning scale; GCGS = gender-

confirming genital surgery; GD = Gender Dysphoria; GID = Gender Identity Disorder; GIDAANT = Gender Identity Disorder of Adolescence and Adulthood, Nontranssexual type; HADS = Hospital Anxiety and Depression Scale; HAD-A = HAD-Anxiety, subscale to HADS; HAD-D = HAD-Depression, subscale to HADS; ICD-10 = International Classification of Diseases; MINI = Mini International Neuropsychiatric Interview; MMPI-2 = Minnesota Multiphasic Personality Inventory, second version; NR = not reported; RSE = Rosenberg Self-esteem Scale; SADS = Social Avoidance and Distress Scale; SCID-I and II = Structured Clinical Interview for DSM-IV, Axis I and II disorders; SCID-D = Structured Clinical Interview for DSM-IV Dissociative Disorders; SCL-90-R = Symptom Checklist-90 (revised); SES = Self-esteem scale; SF-36 = Short Form 36-item Questionnaire; SSEI = Social Self-esteem Inventory; TM = Transgender men; TW = Transgender women; y = year; [1,2,3] Studies using same data; [4] age at time for permission for sex reassignment surgery.