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Gender dysphoria: Insights on etiology, treatment safety, and outcomes

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Abstract

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Gender dysphoria (GD) is defined as significant distress or impairment caused by the discrepancy between an individual's experienced gender and the sex assigned at birth. This work explores the etiology, treatment safety, and outcomes of GD through four studies.

Study I utilizes a population-based approach to analyze the prevalence of GD in twins, using data from a Swedish population-based cohort from 2001 to 2016. The objective is to assess the influence of genetic and environmental factors on the development of GD by comparing its prevalence in different-sex twins, same-sex twins, and non-twin siblings. The results indicate a higher prevalence of GD in different-sex twins (37%) compared to same-sex twins (0%) and non-twin siblings (0.16%), suggesting a potential influence of intrauterine factors in the development of GD.

Study II focuses on evaluating the occurrence of IIH in individuals undergoing treatment with GnRHa for GD in Sweden between 2006 and 2016. The study did not observe any cases of IIH within the cohort of 410 individuals with GD who received GnRHa treatment. While better-powered studies are needed to clarify any potential association between GnRHa and IIH, the study results do not present substantial evidence to support an association.

Study III examines associations between perinatal factors and GD using a matched case-control design with 7,432 individuals with GD and 72,136 individuals without GD. Very preterm birth, low birth weight, small head circumference, and being small for gestational age were associated with increased odds of GD. ASD was present in 31% of individuals with GD versus 3.5% of controls. Mediation analysis revealed that ASD fully mediated the associations between several perinatal factors (Apgar score at 5 minutes, birth length, head circumference, small for gestational age, and fetal growth restriction percentile) and GD, suggesting that perinatal risk factors may influence GD development primarily through pathways involving ASD.

Study IV examines pregnancy and childbirth outcomes among TGD individuals in Sweden using national registry data from 2001-2023. The study included 198 TGD individuals with 303 deliveries, categorized into three cohorts: deliveries before GD diagnosis (n=186), after diagnosis without testosterone treatment (n=86), and after diagnosis with testosterone treatment history (n=31), compared to 1,187 cisgender individuals with 2,289 deliveries. The pre-diagnosis cohort showed higher socioeconomic vulnerability, including higher rates of teenage pregnancy, lower income and education levels, and higher smoking rates, along with higher preterm birth rates (15% vs 5.8% in cisgender controls) and low birth weight (7.5% vs 3.8%). Post-diagnosis cohorts showed outcomes generally comparable to controls, though all TGD cohorts had elevated rates of elective cesarean sections (16-28% vs 9.3% in cisgender). No adverse effects of having received testosterone treatment on birth outcomes were observed in the small sample studied.

Keywords: gender dysphoria, gender incongruence, epidemiology

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List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I. Karamanis G, Karalexi M, White R, Frisell T, Isaksson J, Skalkidou A, Papadopoulos FC. (2022) Gender dysphoria in twins: a register-based population study. Scientific Reports, Aug 4;12(1):13439. doi: 10.1038/s41598-022-17749-0. PMID: 35927439; PMCID: PMC9352732.

II. Karamanis G, Frisell T, Holmberg M, Halldin M, Sylvén S, Skalkidou A, Papadopoulos FC. (2023) Incidence of Idiopathic Intracranial Hyperten-sion in Individuals With Gonadotropin-Releasing Hormone Analogue Treatment for Gender Dysphoria in Sweden. JAMA Pediatrics, Jul 1;177(7):726-727. doi: 10.1001/jamapediatrics.2023.0656. PMID: 37126330; PMCID: PMC10152371.

III. Karamanis G, White RA, Arinell H, Clark KD, Frisell T, Cnattingius S, Sylvén S, Skalkidou A, Papadopoulos FC. Perinatal factors and gender dysphoria: a population-based, matched case-control study. *Manuscript*.

IV. Karamanis G, Ohlsson Gotby V, White R, Frisell T, Skalkidou A, Clark KD, Sylvén S, Papadopoulos FC. Pregnancy and childbirth outcomes in transgender and gender diverse individuals in Sweden. *Manuscript*.

Contents

Abbreviations

AFAB	Assigned female at birth
AMAB	Assigned male at birth
ASD	Autism spectrum disorder
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CI	Confidence interval
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DZ	Dizygotic
FDA	Food and Drug Administration
FGR	Fetal growth restriction
GAHT	Gender-affirming hormone therapy
GD	Gender dysphoria
GID	Gender identity disorder
GnRHa	Gonadotropin-releasing hormone analogues
ICD-10	International Classification of Diseases, 10th Revision
ICD-11	International Classification of Diseases, 11th Revision
IIH	Idiopathic intracranial hypertension
LISA	Longitudinal Integrated Database for Health Insurance and Labour Market Studies
MBR	Medical Birth Register
MGR	Multi-Generation Register
MZ	Monozygotic
NPR	National Patient Register
OR	Odds ratio
PDR	Prescribed Drugs Register
SGA	Small for gestational age
TGD	Transgender and gender diverse
TPR	Total Population Register

Introduction

Gender Dysphoria and Related Terminology

The terminology used to describe individuals with gender dysphoria varies considerably across research, reflecting evolving diagnostic systems and community preferences, making comparison across literature challenging. Gender dysphoria (GD) is defined in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as significant distress or impairment in social, occupational, or other important areas of functioning, resulting from a pronounced and persistent incongruence between an individual's experienced gender and their sex assigned at birth (1).

In the 10th Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), the condition was previously classified under the term 'Gender Identity Disorders' (2), where 'F64.0 Transsexualism' has been the main diagnostic code used for GD. However, the 11th Revision (ICD-11) has moved away from viewing the condition as a mental disorder and reclassified it to a new chapter on conditions related to sexual health (3). ICD-11 now defines it as 'gender incongruence,' described as a pronounced, persistent incongruence between the individual's experience of gender and the sex assigned at birth (3).

Gender incongruence refers to the mismatch between experienced and assigned gender, regardless of whether it causes distress. Gender identity is a person's deeply-felt, inherent sense of being male, female, or an alternative gender. Gender dysphoria specifically denotes the clinical condition where the incongruence results in significant distress or impairment.

Terminology Used in This Thesis

In this thesis, *individuals with gender dysphoria (GD)* refers to those with a clinical diagnosis according to ICD-10 codes recorded in Swedish national health registers. *Transgender and gender diverse (TGD)* is a broader term encompassing individuals whose gender identity differs from their sex assigned at birth. All four studies rely on register-based data, identifying individuals through clinical diagnoses recorded in healthcare settings—capturing those who sought healthcare and received a diagnosis, not all individuals who may experience gender diversity. The findings apply specifically to clinically diagnosed GD and should not be generalized to gender identity or gender diversity more broadly, as these are related but distinct concepts. The term *cisgender* in Study IV describes the comparison group (individuals without a GD diagnosis) as a descriptive convention, not verified gender identity. The gender identity of individuals in either group is not known and no assumptions are made about it.

Epidemiology

The prevalence of GD has been observed to vary widely due to different methodologies and populations employed in various studies. The measured outcomes in these prevalence studies are often diverse, encompassing GD, gender incongruence, and gender identity, which can contribute to the observed variations in prevalence rates. Nonetheless, recent trends suggest a marked increase in the incidence and prevalence of GD since the 2000s, especially during the 2010s, both in Sweden and internationally (4).

Health system-based studies relying on diagnostic codes typically report the lowest prevalence estimates, ranging from 0.02% to 0.1% (5). Survey-based studies assessing self-reported transgender identity yield higher estimates. A recent systematic review found that when narrower definitions of transgender identity are used, prevalence rates range from 0.3% to 0.5% among adults and 1.2% to 2.7% among children and adolescents, with overall estimates across age groups of 0.5% to 1.3% (6,7). When broader definitions encompassing various manifestations of gender diversity are applied, prevalence estimates increase to 0.5% to 4.5% among adults and 2.5% to 8.4% among children and adolescents (6).

Etiology

The traditional approach to understanding GD has often relied on normative sex-dimorphic psychosexual differentiation models. These models posit that biological and psychological processes guide the development of gender identity in a way that is typically aligned with one's sex assigned at birth (8). In the case of GD, these processes are thought to operate differently, leading to a mismatch between an individual's experienced gender and their assigned sex. This view has garnered support from a range of research, based partially on animal studies that examine sex-specific behavior, although, importantly, animal studies do not directly study concepts of gender identity or GD.

Some argue for the validity of alternative explanations, such as within-sex models. These models suggest that variations in gender identity can occur within the same sex without being caused by a 'reversal' of typical psychosexual development (9). Instead, factors like hormonal variations, socialization, or life experiences could contribute to the development of GD within the context of the same biological sex.

Hormonal theories focus on the role of prenatal exposure to sex hormones (10,11), positing that atypical sexual differentiation of the brain may contribute to GD. Neuroimaging studies have supported this to some extent by showing both structural and functional differences in the brain between individuals with GD and cisgender controls (12,13). However, these findings are not conclusive and may be influenced by various factors such as sexual orientation and age of onset.

Psychosocial theories have also been proposed, emphasizing the role of early childhood experiences in the formation of gender identity (14–16). Yet, these theories face methodological challenges, including the difficulty of collecting reliable retrospective data and the lack of a comparison group.

The stability of gender identity, particularly in children and adolescents, is also being reconsidered. While traditionally viewed as a stable trait, emerging finding (17–19) have suggested that gender identity might be more fluid, influenced by a combination of individual and contextual factors, and that early experiences and transitions may play a role in its course.

An alternative hypothesis, among several less well-established theories, suggests that gender incongruence might arise from a disconnection between cerebral circuits that mediate self-perception and those that govern body perception (13,20).

The role of genetics in the etiology of GD, has been explored through family and twin studies. The twin study design, in particular, serves as a particularly useful tool in assessing the roles of genetics and environment on physical and behavioral traits. Monozygotic (MZ) twins share the same genotype, whereas dizygotic (DZ) twins are as genetically similar as non-twin siblings, sharing approximately 50% of their genes. Under the equal environments assumption, both types of twins are expected to be equally exposed to environmental influences. Comparing concordance rates between MZ and DZ twins can thus provide insights into the heritability of a particular trait, including GD.

However, the majority of genetic studies (Table 1), have been somewhat limited by sample sizes, selection biases, and examined related constructs such as gender identity, gender diversity, or gender nonconformity, rather than GD specifically (16,21–23). The evidence points to gender identity, and possibly GD, being likely polygenic, influenced by multiple genes and possibly shaped by environmental factors, though findings remain inconsistent due to methodological differences.

The focus of multiple studies on outcomes like gender nonconformity, which has been shown to be primarily associated with sexual orientation rather than gender identity or GD (16,21), makes it a less appropriate measure of the latter. The few twin studies that have focused on GD have shown variable heritability rates. For example, Coolidge et al. estimated heritability at 62% (23), while Sasaki et al. found heritability rates of 41% for adolescent assigned females and 11% for adult assigned females, with no genetic effects found for assigned males (24). Other studies, like Heylens et al., reported a concordance rate of 39.1% in MZ twins and 0% in DZ twins (22). However, a limitation of this study was that it combined multiple published case reports and a clinical sample, which may affect the generalizability and interpretation of the concordance rates.

Table 1. Studies examining gender identity-related outcomes in twin and non-twin siblings

Study	Method	N	Outcome	Findings	Comments
Bailey et al.	Heritability of childhood gender non-conformity and adult masculinity–femininity in twins	1341 assigned male (aM) and 2441 assigned female (aF) twin pairs	Childhood gender non-conformity; continuous gender identity	Heritability for aM 0.50 and for aF 0.37	Retroactive assessment in adults
Coolidge et al.	Heritability of gender identity disorder (GID) in twins	157 twin pairs	Six GID items based on DSM-IV criteria	Heritability of clinically significant GID 0.62	Children and adolescents
Knafo et al.	Heritability of atypical gender role development in twins	5799 twin pairs	Masculinity and femininity; 24 items of preschool activities inventory	Group heritability for aM 0.26-0.27 and for aF 0.42-0.50	Children 3-4 years
van Beijsterveldt et al.	Heritability of cross-gender behavior during childhood in twins	4530 aF twin pairs	Cross gender behavior & cross gender identity	Genetic factors accounted for 70% of cross-gender behavior	Children 7 and 10 years
Alanko et al.	Heritability of cross-gender behavior during childhood in twins	3261 twins	Shortened version of the Recalled Childhood Gender Identity/Gender Role Questionnaire	Heritability estimates for childhood gender atypical behavior 51% for aF and 29% for aM	Adults, recalled childhood atypical gender behavior before the age of 12 years
Gómez-Gil et al.	Concordance for GID in twin and non-twin siblings	995 patients	GID according to DSM-IV and ICD-10, assessed	12 non-twin and 2 twin pairs concordant for GID	Patients from gender identity clinics

			with semi-structured clinical interviews and case discussion		
Burri et al.	Heritability for childhood gender typicality in twins	4426 twins	Childhood gender typicality; Four items assessing childhood sex-typed behavior and gender identity	Heritability for childhood gender typicality was 32% and for adult gender identity 11%	Adults, same-sex pairs (aF)
Heylens et al.	Concordance for GID in twins	51 twin pairs	GID as reported in previous case reports or own assessment	Concordance among monozygotic twins 39.1% and among same and different-sex DZ twins 0%	Previous case reports and own unpublished cases
Diamond	Concordance for GID in twins	112 twin pairs	Transitioning from living in the gender assigned at birth to that of the opposite gender, self-reported or clinical confirmed	Concordance among same-sex DZ pairs 33% for aM and 23% for aF	Age >10 years, combined from bibliography and survey
Sasaki et al.	Heritability of GID in twins	1961 aM and 2333 aF twin pairs	GID trait score, assessed with questionnaire items, based on DSM-IV	Heritability among aF in adults was 11%	Children, adolescents, and adults

Beyond twin studies, there have also been reports of familial cases of GD, including non-twin siblings and father-child pairs (14). For example, a Spanish study involving 995 individuals with GD reported 12 pairs of GD in non-twin siblings (15). The probability of a sibling having GD was found to be higher for siblings of transgender individuals assigned males at birth than for those assigned females at birth. This pattern contrasts with some twin studies, such as Sasaki et al., which reported higher heritability estimates for individuals assigned female at birth.

Further, studies on gene polymorphisms of sex hormone receptors suggest a potential influence on estrogen and testosterone receptors, potentially impacting brain development and contributing to gender incongruence (25,26).

In conclusion, the findings of previous genetic studies regarding the etiology of GD point to intricate interactions between both genetic and environmental factors. However, the evidence supporting a genetic etiology for GD remains tentative, due to differences in study design, definitions, assessment measures, and the consideration of potential confounding variables.

Neurodevelopmental Overlap and Autism Spectrum Disorder

An emerging area of research has identified a substantial overlap between GD and neurodevelopmental disorders, particularly autism spectrum disorder (ASD) (21). ASD is a neurodevelopmental condition that affects sensory processes, social cognition, and other traits that may overlap with gender identity development and one's experience of gender as a social construct.

The co-occurrence of ASD and GD has been well established. Recent meta-analyses indicate that the prevalence of ASD diagnoses among individuals with GD is substantially higher than in the general population, ranging from 6% to 26%, with pooled estimates around 11%, compared to approximately 1% in the general population (27), although the severity of ASD varies. Conversely, both gender diversity and gender dysphoria are more common among autistic individuals than in the general population. In adults, gender diversity is seen in 5.4% of autistic versus 0.7% of non-autistic individuals, and in children, gender dysphoria is reported in 4.0% of autistic versus 0.7% of non-autistic children (28,29).

Psychological and social hypotheses have been proposed to explain this co-occurrence. These include cognitive rigidity and differences in social communication associated with ASD, which may influence gender identity development, as well as reduced sensitivity to social norms and expectations regarding gender (30). Social challenges, experiences of marginalization, and difficulties with peer relationships may also contribute to the higher prevalence of gender diversity among autistic individuals. Additionally, ascertainment bias, whereby autistic individuals are more likely to come into contact with clinical services, could partially explain the observed co-occurrence (27).

Beyond these psychological and social factors, hypotheses about shared neurodevelopmental mechanisms have been proposed, suggesting that both conditions may be influenced by atypical brain development or connectivity during critical periods (30,31). Given the established role of perinatal factors in neurodevelopmental outcomes, it has also been hypothesized that certain perinatal factors may be associated with gender dysphoria development through such pathways (31).

Understanding the relationship between ASD and GD is important not only for elucidating potential etiological pathways but also for clinical care, as individuals presenting with both conditions may have specific needs that require tailored approaches.

Treatment Safety

The management of GD has evolved to a multi-disciplinary approach that follows guidelines from the World Professional Association for Transgender Health (WPATH) (8). These guidelines outline gender-affirming treatments to help align physical characteristics with gender identity. While protocols are increasingly tailored to individual needs, they typically involve a combination of established interventions, such as puberty blockers, hormone therapy, gender-affirming surgery, speech therapy, hair removal, and other aids for gender affirmation.

As the demand for gender-affirming care continues to rise, research in this area has also expanded, with most studies originating from Northern Europe and the United States. Although questions remain about the universal applicability of these findings, the general consensus strongly supports the safety and effectiveness of gender-affirming hormone therapy (GAHT) (32).

GAHT has been shown to have a range of positive effects, significantly reducing symptoms of gender dysphoria and alleviating mental health issues such as depression and anxiety, primarily by reducing distress. This is consistent across various studies, which report improvements in well-being and potential reductions in anxiety, especially for individuals undergoing masculinizing hormone therapy (33). The therapy facilitates desired physical changes, aiding in achieving a more congruent gender presentation, and has been linked to improved social functioning and reduced rates of comorbidities such as depression, anxiety, suicidality, and substance use disorders (5,34,35). However, the results on GAHT's impact on quality of life and interpersonal functioning are somewhat inconclusive and hint towards both improvements and potential challenges (33,36).

In the context of treating adolescents with GD, pubertal suppression is a possible approach. Often initiated following the guidelines of the Dutch protocol (37), this treatment employs Gonadotropin-Releasing Hormone analogues (GnRHa) to delay the physical changes of puberty. This allows these young individuals more time to explore their gender identity.

While this approach is generally considered safe, there are concerns about its potential long-term effects, such as reduced bone density and negative impact on cognitive development (38). Ongoing research and medical monitoring are considered important to gain a comprehensive understanding of these potential risks.

In 2022, the U.S. Food and Drug Administration (FDA) issued an update to its safety guidelines for GnRHa (39). This update included warnings about the potential risk of idiopathic intracranial hypertension (IIH), a condition characterized by elevated cerebrospinal fluid pressure leading to severe headaches and possible vision impairment (40). The warning was based on post-marketing surveillance data reporting six cases of IIH following GnRHa treatment. IIH is a rare condition with an adult incidence in Sweden of approximately 0.71 per 100,000 population, with a female-to-male ratio of about 6:1 (41,42). Understanding the true risk of IIH in individuals with GD receiving GnRHa treatment is important for informed clinical decision-making.

Pregnancy outcomes in transgender and gender diverse individuals

Transgender and gender diverse (TGD) individuals assigned female at birth (AFAB) are typically born with anatomy that allows them to become pregnant and give birth. Recent research indicates that approximately one-tenth of AFAB TGD individuals experience pregnancy during their lifetime. Over the last decades, a substantial increase in the number of individuals of reproductive age seeking transgender healthcare has been observed internationally (43). Consequently, pregnancy-related care will be needed by an increasing number of TGD individuals.

However, it is unclear whether pregnancy-related outcomes differ between TGD individuals compared to those of cisgender women. Pregnancy and delivery are demanding periods for any birthing individual. For TGD individuals, these periods may present additional challenges, including barriers to accessing pregnancy-related healthcare due to lack of provider knowledge, fear of discrimination, and systemic obstacles (32,33,36). TGD individuals may also experience exacerbated levels of gender dysphoria due to pregnancy-related changes (37,38). Combined, these factors may cause increased levels of stress, which has been associated with worse pregnancy outcomes for both the birthing parent and the child (44–46).

There are also concerns that some gender-affirming treatments, such as testosterone, might compromise fertility and pregnancy outcomes. For many TGD individuals, the need for gender-affirming treatments is both necessary and urgent. For some, the desire for gender-affirming hormone therapy may be perceived as an obstacle that conflicts with their fertility or family-building intentions and vice versa (47).

While there is a growing body of qualitative research exploring the challenges TGD individuals face in utilizing pregnancy healthcare (32,36,37,48,49), quantitative studies on birth outcomes have been limited, with most research based on data from the United States (50–52). This reliance on a single national context represents a major gap in the literature, as differences in healthcare systems, insurance models, legal frameworks, and socio-cultural environments limit the generalizability of findings to other settings.

Aims

The overall aim of this thesis is to improve understanding of the etiology, treatment safety, and pregnancy outcomes in gender dysphoria using Swedish population-based register data.

1. Examine concordance for GD diagnosis in twin pairs of same and different sex, as well as in non-twin sibling pairs, in Sweden.
2. Assess the incidence of idiopathic intracranial hypertension (IIH) in individuals diagnosed with GD in Sweden, with and without gonadotropin-releasing hormone analogue (GnRHa) treatment.
3. Examine the associations between perinatal factors and GD, and assess whether autism spectrum disorder (ASD) mediates these relationships.
4. Examine pregnancy and childbirth outcomes among transgender and gender diverse (TGD) individuals assigned female at birth in Sweden.

Materials and Methods

Design

All four studies were designed as observational studies based on cohort data from the Swedish national registers. Study I utilized a population-based cohort design to examine familial aggregation of GD. Study II employed a matched cohort study design to assess IIH incidence. Study III used a matched case-control design to examine associations between perinatal factors and GD. Study IV used a cohort design to compare pregnancy outcomes across different TGD and cisgender cohorts.

Data Sources

Data were primarily sourced from the National Patient Register (NPR), the Medical Birth Register (MBR) and the Prescribed Drug Register (PDR). Additionally, data were collated from the Total Population Register (TPR), the Swedish Multi-Generation Register (MGR), and the Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA).

The NPR comprises information on primary and secondary ICD diagnoses from visits to specialist outpatient care since 2001 and inpatient healthcare since 1964, including surgeries, admission, and discharge dates. The inpatient register has nationwide coverage since 1987, while the outpatient register started with coverage between 8 and 18% during the period 2001–2003 and reached 93% coverage by 2015 for psychiatric diagnoses (4).

The MBR, established in 1973, records data on all live births and stillbirths in Sweden. For stillbirths, from July 2008 forward, the register includes cases from 22 weeks of gestation onwards. Prior to July 2008, only stillbirths from 28 weeks of gestation were recorded. The register contains comprehensive information about pregnancy outcomes and perinatal health indicators, with excellent coverage of key perinatal outcomes and minimal missingness for critical variables like birth weight and gestational length.

The PDR includes data on all redeemed medication since July 1, 2005. The TPR contains information on birth dates, sex assigned at birth, change of legal sex, country of birth, and education level. The MGR allows the linkage of individuals born in 1932 and later to parents, siblings, and offspring. LISA contains information on educational attainment, civil status, income, and employment of all residents of Sweden.

Study Population

Study I

For Study I, the source population comprised individuals with a new diagnosis of GD between January 1, 2001, and December 31, 2016, who were at least 10 years old. A total of 4,374 individuals met these criteria.

Individuals with prior GD diagnoses under the older ICD-8 and ICD-9 coding systems were excluded from the study, numbering 100 subjects. Individuals who had undergone a legal change of sex prior to receiving a GD diagnosis were also omitted, accounting for 22 individuals. Additional exclusions were made for individuals who had received any form of surgical or hormonal gender-affirming treatments prior to their first GD diagnosis, eliminating an additional 166 subjects from the cohort.

To define individuals with GD, the criteria proposed by Indremo et al. (4), shown to accurately identify clinically relevant GD in the Swedish context, were applied. The study considered those who had received an ICD-10 GD diagnosis (F64.0 Transsexualism, F64.8 Other gender identity disorders, or F64.9 Gender identity disorder, unspecified) in the NPR on at least four separate occasions or those who received at least one GD diagnosis followed by gender-affirming treatment. The incorporation of the first definition aimed to include individuals with clinically significant GD who did not receive gender-affirming treatment for various reasons, while the latter definition ensured the inclusion of those with treated GD but with too short a follow-up time to obtain four diagnoses. Consequently, 2,592 individuals were identified with GD according to this definition. Out of these, 1,536 had at least one full sibling, yielding 2,601 siblings.

Twins were defined as full siblings born in the same year and month as the proband (the individual with gender dysphoria). Both twin and non-twin pairs are not unique given that a pair of two siblings (e.g., A and B) would appear twice, if they both have a GD diagnosis, because each individual would be proband for its sibling (A–B and B–A).

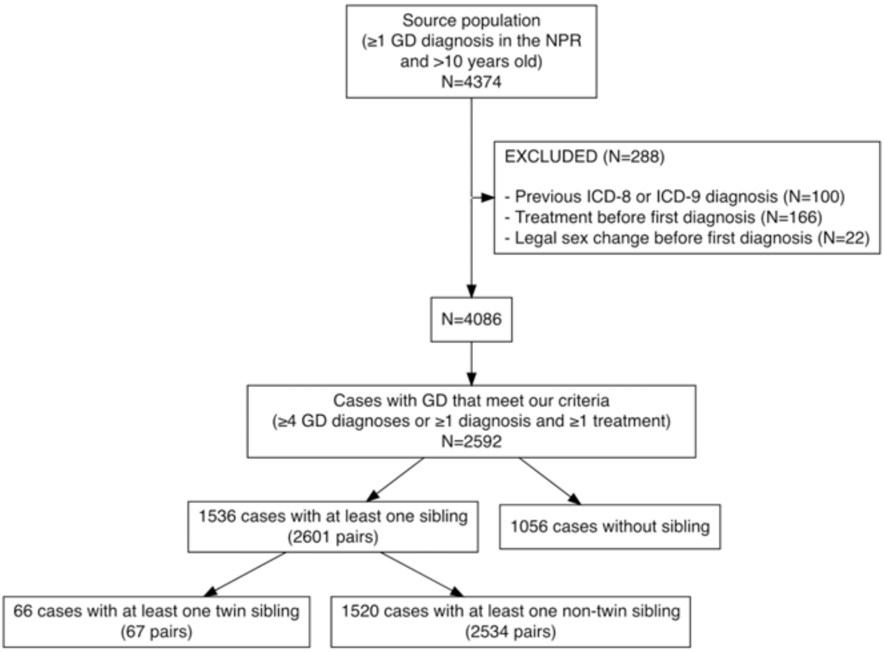

Figure 1. Flowchart of the study population selection

Study II

In Study II, 4,230 individuals with at least one GD diagnosis between 2006 and 2016 were identified. For each individual with a GD diagnosis, up to 20 matched individuals without a GD diagnosis were selected based on age, same and opposite sex assignment at birth, and county of residence.

The study population was divided into three cohorts. The first cohort included 410 individuals with GD who received GnRHa. The second cohort comprised 3,820 individuals with GD who did not receive GnRHa. Additionally, a general population cohort without GD and without GnRHa treatment consisted of 73,096 individuals.

Table 2. Description of the Subcohorts, Inclusion and Exclusion Criteria, and Entry and End Dates of Follow-up Used to Calculate Person-Time of Exposure

Cohort	Inclusion criteria	Exclusion criteria	Entry date	End date
GD with GnRHa	At least one GD diagnosis (any of the ICD-10 codes F64.0, F64.8 or F64.9) in the NPR and treatment with GnRHa (ATC codes H01CA and L02AE in the PDR) after or within 2 years before the first GD diagnosis	IIH diagnosis (ICD-10 code G93.2 in the PNR) before GD diagnosis*	Date of first dispensed prescription for GnRHa	The earliest of: Date of first IIH diagnosis, date of death, date of emigration, or end of study period (2016-12-31)
GD without GnRHa	At least one GD diagnosis	IIH diagnosis (ICD-10 code G93.2 in the PNR) before GD diagnosis*	Date of first GD diagnosis	The earliest of: Date of first IIH diagnosis, first dispensed GnRHa prescription, date of death, date of emigration, or end of study period (2016-12-31)
General population without GD	20 randomly selected individuals from the general population for each selected individual with GD, matched for age, same and opposite assigned sex at birth and county of residence	Lifetime GD diagnosis. IIH diagnosis (ICD-10 code G93.2 in the PNR) before entry date. GnRHa prescription before entry date.	Date of first GD diagnosis of their matched person	The earliest of: Date of first IIH diagnosis, first dispensed GnRHa prescription, date of death, date of emigration, or end of study period (2016-12-31)

To mitigate immortal time bias, the start of follow-up for the unexposed cohorts was aligned with the exposure period of the GnRHa cohort. Specifically, individuals in the GD without GnRHa cohort and the general population cohort entered follow-up at dates corresponding to when matched individuals in the GnRHa cohort received their first prescription. This ensured that all cohorts had comparable risk periods and avoided the bias that would arise from counting person-time before treatment as unexposed time.

Study III

The Study III population included all individuals who had a GD diagnosis (ICD-10 codes F64.0, F64.8, or F64.9) recorded in the NPR between 2001 and 2023, were at least 10 years old at the time of first diagnosis and were born in Sweden from 1973 onwards. For each individual with GD, up to 10 controls of the same sex assigned at birth were randomly selected from the TPR, matched on birth year and county of residence at the time of first diagnosis within the study period. Controls had to be alive and residing in Sweden at the time of the matched case's diagnosis date. An individual could serve as a control to multiple cases.

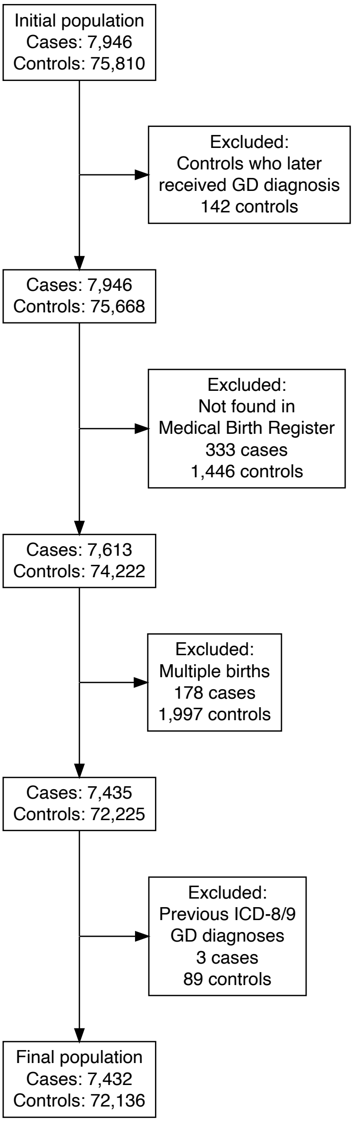

Figure 2. Flow chart of study population selection for Study III

The initial sample comprised 7,946 individuals with GD and 75,810 controls. After excluding 142 controls who later received a GD diagnosis, 333 individuals with GD and 1,446 controls not found in the Medical Birth Register, multiple births (178 individuals with GD and 1,997 controls, excluded due to known data quality issues in the Medical Birth Register, where same-sex twins may be incorrectly matched to their sibling's medical record data and parity information for multiple births is unreliable), and cases and controls with previous GD diagnoses under ICD-8/9 (3 individuals with GD, 89 controls), the final study population consisted of 7,432 individuals with GD and 72,136 controls.

Study IV

The Study IV base cohort comprised all transgender and gender diverse (TGD) individuals (N=10,614; 5,908 assigned female at birth [AFAB]) who received a gender dysphoria (GD) diagnosis (ICD-10 codes F64.0, F64.8, or F64.9) recorded in the National Patient Register (NPR) between 2001 and 2023, and who were at least 10 years old at the time of first diagnosis. For each TGD individual, up to 20 cisgender controls without a GD diagnosis at the time of the TGD individual's first diagnosis were selected from the Total Population Register (TPR), matched on birth year, same- and opposite-sex assignment, and county of residence (N=206,754; 103,283 AFAB).

All deliveries of AFAB TGD individuals and AFAB controls registered in the Medical Birth Register (MBR) between 2001 and 2023 were included (N=53,664). To ensure complete capture of testosterone exposure history and minimize misclassification, individuals whose first GD diagnosis occurred before July 1, 2005 (the start of the Prescribed Drug Register [PDR]) were excluded from the analytic sample. As a result, only individuals with a first GD diagnosis on or after July 1, 2005 were eligible, but included deliveries could have occurred before this date.

The remaining deliveries (N=2,592) were categorized into four mutually exclusive cohorts based on the timing of delivery relative to GD diagnosis and testosterone treatment:

(1) Deliveries before the individual's first GD diagnosis (n=186 deliveries from 120 individuals), (2) deliveries at or after the first GD diagnosis but with no recorded testosterone treatment before delivery (n=86 deliveries from 56 individuals), (3) deliveries after both the first GD diagnosis and first recorded testosterone treatment (n=31 deliveries from 22 individuals), and (4) deliveries of the cisgender controls (n=2,289 deliveries from 1,187 individuals).

Exposures

Study I

The primary exposure of interest was sibling type—being a different-sex twin, same-sex twin, or non-twin sibling—to a proband with gender dysphoria (GD), as identified in the National Patient Register using ICD-10 diagnostic codes. Other measured variables included age at the time of GD diagnosis, sex assigned at birth, education level, and country of birth.

Study II

The primary exposure was the use of GnRHa for the treatment of GD. The study identified individuals who had received at least one prescription of GnRHa between 2006 and 2016. GnRHa treatments were identified by ATC codes H01CA and L02AE in the PDR. Other measured variables for Study II included age at the time of GD diagnosis, sex assigned at birth, age at the time of IIH diagnosis, and follow-up time.

Study III

Perinatal exposures were grouped into two main categories: child-related variables and maternal variables.

Child-related variables included birth weight, birth length, head circumference, gestational age, Apgar score at 5 minutes, small for gestational age (SGA) status, and the fetal growth restriction (FGR) index. SGA was defined as a birth weight more than 2 standard deviations below the mean for gestational age. The FGR index was calculated as the ratio of actual to expected birth weight (the latter derived from a sex-specific polynomial function of gestational age in days), and categorized by percentiles.

Maternal variables included season of birth, parity, maternal age, delivery mode, maternal BMI at admission to prenatal care, previous miscarriages, maternal hypertension, maternal diabetes, maternal smoking at admission to maternity-care services, maternal infertility treatment, maternal country/region of birth.

ASD was operationalized using diagnoses in the NPR with ICD-10 codes F84 and ICD-9 codes 299A–299X.

Study IV

The primary exposure was transgender and gender diverse (TGD) status, operationalized as having a diagnosis of gender dysphoria (GD) recorded in the National Patient Register (ICD-10 codes F64.0, F64.8, or F64.9) at age 10 years or older. Deliveries were categorized by timing relative to the first GD diagnosis and by history of testosterone treatment (before or after first recorded testosterone dispensation in the Prescribed Drug Register, ATC code G03B). The comparison group comprised cisgender individuals, defined as those without a GD diagnosis at the time of the matched TGD individual's first diagnosis, matched on birth year, sex assigned at birth, and county of residence.

Outcome Measures

Study I

The primary outcome was the prevalence of GD, defined either by receiving a GD diagnosis on at least four occasions or by receiving at least one GD diagnosis followed by gender-affirming treatment, among twin and non-twin siblings to probands with GD.

Study II

The primary outcome was the incidence rate of IIH, designated by the first ICD-10 diagnosis G93.2 in inpatient or specialist outpatient care.

Study III

The primary outcome was diagnosis of GD.

Study IV

The primary outcomes included pregnancy and childbirth outcomes: preterm birth, low birth weight, birth length, head circumference, small for gestational age status, mode of delivery (including elective and emergency cesarean sections).

Statistical Analyses

For all studies, statistical analyses were executed using the R language. Ethical approval was obtained from the Central Ethical Review Board in Stockholm (Dnr. Ö30-2016).

Study I

In the first study, the population was described through descriptive statistics. The percentage of probands with a twin or non-twin sibling with GD was computed, segmented by the sex assigned at birth. Statistical significance was established using Fisher's exact test and Mann–Whitney U test, with alpha set at 0.05.

Study II

For the second study, the primary analytical focus was the calculation of incidence rates of IIH, and their 95% Confidence intervals. The latter were computed under the assumption of a Poisson distribution.

Study III

Descriptive analyses of all variables were performed, comparing individuals with GD and controls. Conditional logistic regression conditioned on the matched case-control sets with robust standard errors clustered over these matched sets was employed to examine the association between perinatal factors and GD. Initially, crude univariable analyses were performed for each child-related factor. Subsequently, adjusted analyses were conducted to control for potential confounding, adjusting for region of birth and maternal factors (season of birth, parity, maternal age, delivery mode, maternal BMI, miscarriages, maternal hypertension, maternal diabetes, maternal smoking, maternal infertility treatment, and maternal birthland).

For binary variables, statistical significance was assessed using the Wald test. For categorical variables with three or more levels, overall significance was assessed using the likelihood-ratio test. To account for multiple testing, p-values were adjusted using the false discovery rate (FDR) method with an FDR of 5%.

Causal mediation analyses were conducted using standard logistic regression models within a counterfactual framework to examine the potential mediating role of ASD in the association between perinatal factors and GD. The effects were estimated using nonparametric bootstrapping with 1 000 simulations, as implemented in the R mediation package (53,54). Seven separate models were constructed, one for each child-related perinatal factor (Apgar score at 5 minutes, birth weight, birth length, head circumference, SGA status, FGR percentile, and gestational age) as independent variables, GD diagnosis as the outcome, and ASD diagnosis as the mediator. Given the binary nature of the outcome, and because GD is a rare outcome, the odds ratio estimates produced by the logistic regression models approximate the risk ratio, which is necessary for the interpretation of effect estimates within this framework. Average causal mediation effects, average direct effects, and total effects were estimated with 95% confidence intervals.

Study IV

Categorical variables were compared between each of the three GD cohorts and the cisgender cohort using Fisher's exact test. Confidence intervals for the proportions were calculated using the Agresti-Coull method. Statistical software R version 4.5.0 was used with tidyverse and gtsummary packages.

Results

Study I

In Study I, data from a large Swedish population-based cohort collected over a 16-year period (2001-2016) were analyzed to investigate the prevalence of GD among different categories of siblings: different-sex twins, same-sex twins, and non-twin siblings. The study included 67 twin pairs and 2,534 non-twin siblings.

Among different-sex twins, 10 out of 27 pairs (37.0%) showed concordance for GD, meaning both twins had a GD diagnosis. In contrast, among the 40 same-sex twin pairs, none (0%) showed concordance for GD. Among non-twin siblings, 4 out of 2,534 siblings (0.16%) of probands with GD also had a GD diagnosis. The difference in concordance between different-sex twins and same-sex twins was statistically significant ($p<0.001$).

Study II

In Study II, a register-based study covering a 10-year period in the entire Swedish population was performed. The study focused on the incidence of IIH among individuals with GD who were treated with GnRHa. The GD cohort exposed to GnRHa included 410 individuals, with a median age of 17.8 years. Of these, 211 (51%) were assigned female at birth and 199 (49%) were assigned male at birth. This cohort was compared to 3,820 individuals with GD not exposed to GnRHa, who had a median age of 23.1 years, and 73,096 individuals without GD.

Among the 410 individuals with GD receiving GnRHa, no cases of IIH were identified. The estimated incidence rate was 0.0 per 100,000 person-years (95% CI: 0.0 to 392.0). In contrast, among the 3,820 individuals with GD not receiving GnRHa, 2 individuals developed IIH, with an estimated incidence rate of 15.7 per 100,000 person-years (95% CI: 1.9 to 56.6). Among the 73,096 individuals without GD and not exposed to GnRHa, 8 were diagnosed with IIH, yielding an estimated incidence rate of 3.2 per 100,000 person-years (95% CI: 1.4 to 6.3).

Of the individuals with GD receiving GnRHa, 73% had a follow-up time of at least 240 days after GnRHa start. This duration is significant because, according to the FDA report, all cases of IIH developed within this time frame.

Study III

The Study III population included 7,432 individuals with a diagnosis of GD and 72,136 controls. Among individuals with GD, 4,456 (60%) were assigned female at birth (AFAB), while 2,976 (40%) were assigned male at birth (AMAB). The age at first GD diagnosis was similar in both AFAB and AMAB, with the largest proportion of individuals being diagnosed between 10-19 years (47%). ASD was present in 2,285 (31%) of individuals with GD and 2,536 (3.5%) of controls.

In crude analyses, very preterm birth (<32 weeks; OR: 2.49, 95% CI: 2.03 to 3.96), low birth weight (≤2,499 g; OR: 1.51, 95% CI: 1.33 to 1.71), birth length <49 cm (OR: 1.21, 95% CI: 1.14 to 1.28), head circumference ≤31 cm (OR: 1.46, 95% CI: 1.27 to 1.68), small for gestational age (OR: 1.39, 95% CI: 1.22 to 1.58), and fetal growth restriction percentile under 10% (OR: 1.17, 95% CI: 1.09 to 1.26) were all significantly associated with increased odds of GD.

After adjustment for region of birth and maternal factors, the following associations remained significant: very preterm birth (<32 completed weeks; OR: 2.31, 95% CI: 1.66 to 3.22), low birth weight (≤2,499 g; OR: 1.68, 95% CI: 1.39 to 2.03), birth length <49 cm (OR: 1.14, 95% CI: 1.05 to 1.24), head circumference ≤31 cm (OR: 1.56, 95% CI: 1.26 to 1.93), and small for gestational age (OR: 1.28, 95% CI: 1.05 to 1.56). Those associations remained statistically significant even after FDR correction.

In mediation analyses without covariate adjustment, significant indirect effects through ASD were found for Apgar score at 5 minutes, birth length, and being small for gestational age. After adjusting for covariates, significant indirect effects through ASD were observed for Apgar score at 5 minutes (effect: -0.006, 95% CI: -0.010 to -0.001), birth length (effect: -0.006, 95% CI: -0.009 to -0.001), head circumference (effect: -0.006, 95% CI: -0.011 to -0.001), SGA (effect: 0.012, 95% CI: 0.004 to 0.021), and FGR percentile (effect: -0.012, 95% CI: -0.026 to -0.000). For all these variables, only the indirect effect was significant while the direct effect was not, indicating full mediation by ASD. For birth weight, gestational age, and malformation, there was no evidence of significant mediation or direct effects in the adjusted models.

Table 6. Mediation analysis of perinatal exposures, autism spectrum disorder, and gender dysphoria. Crude and adjusted indirect, direct, and total effects for each perinatal variable, with autism spectrum disorder as mediator

	Crude			Adjusted*		
Variable/Path	Effect	95% CI	p-value	Effect	95% CI	p-value
Apgar at 5 minutes						
Indirect via ASD	-0.003	-0.008, -0.002	**0.002**	-0.006	-0.010, -0.002	**0.006**
Direct	-0.003	-0.008, 0.000	0.080	0.000	-0.005, 0.004	0.896

	Crude			Adjusted*		
Variable/Path	Effect	95% CI	p-value	Effect	95% CI	p-value
Total	-0.006	-0.014, -0.003	**0.000**	-0.006	-0.012, 0.001	0.100
Birth weight						
Indirect via ASD	0.000	-0.001, 0.001	0.984	0.000	-0.002, 0.002	0.920
Direct	0.000	-0.000, -0.000	**0.000**	0.000	-0.000, 0.000	0.880
Total	0.000	-0.001, 0.001	0.992	0.000	-0.002, 0.002	0.920
Birth length						
Indirect via ASD	-0.003	-0.007, -0.001	**0.006**	-0.003	-0.008, -0.001	**0.014**
Direct	-0.004	-0.007, -0.002	**0.000**	-0.001	-0.004, 0.001	0.266
Total	-0.008	-0.012, -0.004	**0.000**	-0.005	-0.011, -0.001	**0.014**
Head circumference						
Indirect via ASD	-0.001	-0.004, 0.001	0.300	-0.006	-0.010, -0.000	**0.016**
Direct	-0.004	-0.008, -0.001	**0.000**	-0.002	-0.007, 0.001	0.176
Total	-0.005	-0.010, -0.001	**0.000**	-0.008	-0.015, -0.001	**0.010**
Small for gestational age						
Indirect via ASD	0.012	0.007, 0.019	**0.000**	0.011	0.003, 0.019	**0.004**
Direct	0.018	0.004, 0.032	**0.008**	0.013	-0.009, 0.035	0.238
Total	0.030	0.016, 0.046	**0.000**	0.024	0.001, 0.047	**0.042**
FGR percentile						
Indirect via ASD	-0.002	-0.009, 0.003	0.500	-0.009	-0.022, -0.000	**0.046**
Direct	-0.012	-0.028, 0.004	0.164	0.002	-0.022, 0.023	0.808
Total	-0.014	-0.032, 0.003	0.108	-0.007	-0.036, 0.016	0.540
Gestational age						
Indirect via ASD	-0.001	-0.004, 0.001	0.394	-0.002	-0.004, 0.002	0.572
Direct	-0.001	-0.001, -0.000	**0.000**	0.000	-0.001, 0.000	0.582
Total	-0.002	-0.005, 0.001	0.152	-0.003	-0.004, 0.002	0.524
Malformation						
Indirect via ASD	0.003	-0.001, 0.007	0.138	0.000	-0.006, 0.005	0.866
Direct	0.006	-0.004, 0.017	0.246	-0.005	-0.021, 0.011	0.522
Total	0.009	-0.003, 0.021	0.112	-0.006	-0.022, 0.011	0.520

Effects estimated with nonparametric bootstrapping with 1,000 simulations. Classification according to the typology proposed by Zhao et al:

Light green = Indirect-only (full) mediation

Light orange = Complementary (partial) mediation

Light blue = Direct-only effect (No mediation)

Light gray = No mediation effect

*Adjusted for assigned sex at birth, birth year, age and year at first GD diagnosis, and the following maternal factors: season of birth, parity, maternal age, delivery mode, maternal BMI, miscarriages, maternal hypertension, maternal diabetes, maternal smoking at admission in maternity-care services, maternal infertility treatment, and maternal birth land.

Study IV

The Study IV analysis included 198 TGD individuals (120 pre-diagnosis, 56 post-diagnosis without testosterone, and 22 post-diagnosis with testosterone) and 1,187 cisgender individuals, accounting for 303 and 2,289 deliveries, respectively.

Significant age differences were found in the pre-diagnosis cohort compared with controls, with higher proportions of teenage pregnancies (≤19 years: 10% vs 1.3% in controls, p<0.001). Education levels differed significantly from controls in the pre-diagnosis and post-diagnosis without testosterone cohorts (both p<0.001), with lower tertiary education rates of 37% and 39%, respectively, compared to 51% in controls. Income distribution showed significant differences, with higher proportions in the lowest income quintile (36% and 35%, respectively) compared to 16% in controls. All TGD cohorts showed significantly higher rates of single parents compared to controls (p<0.001).

Parity differed significantly in all TGD cohorts, with higher rates of first births at 60%, 59%, and 74%, respectively, compared to 46% in controls. Smoking before pregnancy was significantly higher in the pre-diagnosis cohort compared to controls (32% vs 15%, p<0.001), including smoking during weeks 30-32 of pregnancy (12% vs 4.4% in controls, p=0.001). The prevalence of smoking decreased in each following cohort.

Higher preterm birth rates were observed in the pre-diagnosis cohort (15%) than cisgender controls (5.8%, p<0.001). Conversely, lower preterm birth rates (3.5%, p=0.019) were observed in the post-diagnosis without testosterone cohort compared to controls. No significant differences were observed in the post-testosterone cohort (3.2%, p=0.914) compared to controls.

The pre-diagnosis cohort showed higher rates of low birth weight (≤2,499 g) infants (7.5%) compared to controls (3.8%, p=0.006). Similarly, birth length <49 cm was significantly more prevalent in the pre-diagnosis cohort (29%) compared to controls (18%, p<0.001). The pre-diagnosis cohort also showed higher rates of small (≤31 cm) head circumference compared to controls (5.1% vs 2.2%, p=0

Elevated rates of elective cesarean sections were observed in the pre-diagnosis (17%, p=0.016) and post-testosterone cohorts (28%, p=0.008) compared to deliveries in controls (9.3%). Rates in the post-diagnosis without testosterone cohort were also elevated compared to controls, though not statistically significant (16%, p=0.301).

In the post-testosterone cohort, most deliveries (81%) occurred more than 12 months after testosterone was last prescribed. Testosterone prescribed during pregnancy occurred in 13% of the deliveries (n=4) in this cohort. No malformations, including virilization of genitalia, were observed in the post-testosterone cohort.

Discussion

This doctoral thesis examines gender dysphoria through four complementary studies addressing etiology, treatment safety, and pregnancy outcomes. The findings contribute to understanding the complex multifactorial nature of GD while providing evidence relevant to clinical care and epidemiological research.

Etiological Insights: Intrauterine Factors and Neurodevelopmental Pathways

Study I showed a striking pattern of concordance for GD among siblings. While no concordance was observed among same-sex twins (0%), different-sex twins showed substantially higher concordance (37%) compared to non-twin siblings (0.16%). This distinctive pattern cannot be explained solely by genetic or shared childhood environmental factors, pointing instead to the potential influence of intrauterine exposures.

The absence of concordance in same-sex twins contrasts with some earlier studies that suggested higher concordance rates in monozygotic (MZ) twins. Approximately 44% of same-sex twins are expected to be MZ based on Swedish Twin Registry data (55), yet none showed concordance in our study. This divergence from previous findings may reflect several factors. First, most previous twin studies focused on gender identity as a trait or gender nonconformity rather than clinically diagnosed GD. Second, many earlier studies included predominantly childhood-onset cases, whereas the mean age at diagnosis in Study I was 25 and 32 years for discordant and concordant twin pairs, respectively. The effect of genetics on gender identity may change over the lifespan, with heritability potentially attenuated throughout adolescence and adult life.

The higher concordance in different-sex twins raises questions about prenatal factors, particularly variations in hormone levels produced by the co-twin, that might influence GD development. This aligns with theories positing that prenatal sex hormones have organizing effects on brain development, particularly during the second half of pregnancy (56,57). These organizational structures are subsequently activated by sex hormones during puberty. Neuroimaging studies (12,13) have shown that sexually dimorphic brain structures in individuals with GD appear more congruent with gender identity than with sex assigned at birth, possibly reflecting the effects of prenatal hormone exposure.

However, the study also underscores limitations of existing genetic theories in explaining clinically diagnosed GD. While previous studies (16,23,24) have suggested moderate to high heritability in shaping gender identity as a trait, our cohort, with its stringent clinical definition, found no evidence of heritability. This highlights a potential distinction between gender identity development as a dimensional trait and GD as a clinical condition requiring diagnosis and often treatment.

These interpretations should be considered in light of Study I's limitations, including the lack of zygosity data and relatively small sample size, which are discussed in detail in the methodological limitations section. The findings suggest hypotheses for future research rather than definitive causal pathways.

Study III complements these findings by examining perinatal factors and their relationship to GD through neurodevelopmental pathways. The study identified associations between several perinatal factors and GD, including very preterm birth, low birth weight, small head circumference, and being small for gestational age. Notably, ASD was present in 31% of individuals with GD versus 3.5% of controls.

The mediation analyses showed that ASD fully mediated the associations between several perinatal factors (Apgar score at 5 minutes, birth length, head circumference, small for gestational age status, and fetal growth restriction percentile) and GD. For these variables, only the indirect effect through ASD was significant, while the direct effect was not, indicating full mediation. This pattern suggests that perinatal risk factors may influence GD development primarily through pathways involving neurodevelopmental conditions like ASD, rather than through independent direct effects.

The high prevalence of ASD among individuals with GD in this study may reflect selection effects, as individuals with both conditions may be more likely to seek healthcare and receive diagnoses. Additionally, the co-occurrence does not imply that all individuals with GD have neurodevelopmental differences, nor that ASD causes GD. Rather, the findings suggest shared developmental vulnerabilities or pathways that warrant further investigation.

Together, Studies I and III point to the importance of prenatal and perinatal periods in GD development. Study I suggests intrauterine exposures specific to different-sex twin pregnancies, while Study III identifies perinatal factors operating through neurodevelopmental mechanisms. These findings do not preclude other etiological pathways but highlight specific developmental windows and mechanisms deserving focused research attention.

Treatment Safety: GnRHa and Idiopathic Intracranial Hypertension

Study II addressed a clinical safety question following the FDA's 2022 warning about potential IIH risk associated with GnRHa treatment. In a population-based cohort of 410 individuals with GD treated with GnRHa, followed over a decade, no cases of IIH were identified. For comparison, the estimated IIH incidence rate was 15.7 per 100,000 person-years among individuals with GD not receiving GnRHa, and 3.2 per 100,000 person-years in the general population without GD.

The FDA warning was based on postmarketing surveillance data reporting six cases of IIH following GnRHa treatment, with all cases developing within 240 days of treatment initiation. In Study II, 73% of individuals with GD receiving GnRHa were followed for at least 240 days, providing adequate observation time to capture IIH cases if they occurred. Additionally, none of the individuals with precocious puberty—the underlying condition for GnRHa treatment in five of the six FDA-reported cases—developed IIH in our study.

Three factors warrant consideration in interpreting these findings. First, IIH is a rare condition with baseline incidence in Sweden of approximately 0.71 per 100,000 population, predominantly affecting individuals assigned female at birth (female-to-male ratio approximately 6:1). Second, the confidence intervals around our incidence estimates are wide due to the rarity of the outcome, reflecting the limited power to detect small increases in risk. Third, different GnRHa formulations are used in Sweden compared to those specifically mentioned in the FDA warning (only leuprorelin and triptorelin from the FDA list are prescribed in Sweden, along with buserelin and goserelin which were not included in the FDA report), raising questions about whether risk profiles differ by pharmaceutical formulation.

While our study does not provide definitive evidence against any association between GnRHa and IIH, the findings do not provide substantial support for the association in the context of GD treatment. The results support the continued clinical use of GnRHa for GD management while highlighting the need for better-powered studies and continued surveillance to further elucidate any potential risks.

Pregnancy outcomes in transgender and gender diverse individuals

Study IV examined pregnancy and childbirth outcomes among TGD individuals assigned female at birth, comparing three cohorts: deliveries before GD diagnosis, after diagnosis without testosterone treatment, and after diagnosis with testosterone treatment history, compared to deliveries by cisgender controls.

The findings showed patterns of socioeconomic vulnerability and health outcomes varying across the different cohorts. The pre-diagnosis cohort showed higher rates of teenage pregnancy, lower education levels, lower income, higher rates of single parenthood, and higher smoking rates. This cohort also showed elevated rates of adverse birth outcomes, including higher preterm birth, low birth weight, shorter birth length, and smaller head circumference.

In contrast, the post-diagnosis cohorts showed outcomes generally comparable to cisgender controls for most perinatal measures, although smoking rates remained slightly elevated in the post-diagnosis without testosterone cohort (22% before pregnancy, though not statistically significant when compared to controls). The pre-diagnosis cohort represents individuals who gave birth before receiving their GD diagnosis, suggesting that these individuals may experience heightened vulnerability during the pre-diagnosis period, possibly reflecting the stress and challenges associated with unaddressed gender dysphoria, discrimination, or lack of appropriate healthcare access.

All TGD cohorts showed elevated rates of elective cesarean sections compared to controls (16-28% vs 9.3%), with the highest rate in the post-testosterone cohort. This may reflect patient preferences for planned deliveries (37), healthcare provider decision-making, or other factors related to TGD individuals' specific healthcare needs during pregnancy, such as concerns about gender dysphoria during vaginal delivery or previous negative experiences with healthcare settings.

Regarding testosterone exposure, the study found no evidence of adverse effects on birth outcomes in the small sample of deliveries following testosterone treatment (n=31 deliveries). Most deliveries (81%) occurred more than 12 months after testosterone was last prescribed, and while testosterone was prescribed during pregnancy for 13% of deliveries in this cohort, no malformations including virilization of genitalia were observed. These findings, though based on limited numbers, provide some reassurance about pregnancy safety following testosterone exposure.

The study has limitations, including small sample sizes particularly for the post-testosterone cohort, inability to capture detailed information about specific testosterone regimens or timing of discontinuation, and potential unmeasured confounding. Additionally, the PDR limitation (beginning July 2005) means that testosterone exposure before this date was not captured, potentially leading to some misclassification in cohort assignment.

Methodological Strengths and Limitations

This section discusses strengths and limitations common to all four studies, as well as study-specific methodological considerations.

All four studies benefited from the comprehensive Swedish national register infrastructure, enabling population-based designs with minimal selection bias, large sample sizes, and long follow-up periods. Linkage across multiple registers allowed examination of diverse outcomes and covariates while maintaining data quality and completeness.

However, several limitations warrant consideration. First, register-based diagnoses may not capture all individuals with GD, particularly those who do not seek healthcare or who are diagnosed after their respective study periods (2001-2016 for Studies I and II, 2001-2023 for Studies III and IV). Second, the observational nature of these studies precludes causal inference, as associations may be influenced by unmeasured confounding, reverse causation, or selection effects that cannot be fully addressed through statistical adjustment alone. Third, the twin study (Study I) lacked information on zygosity, though assumptions based on sex assignment and Swedish Twin Registry distributions support the conclusions. Fourth, Studies III and IV involved relatively small numbers for some subgroup analyses, limiting power to detect modest effects or examine effect modification. Fifth, the studies could not account for all potential confounders, including information about social support, discrimination experiences, or specific aspects of gender-affirming care beyond medication prescriptions and diagnoses.

Regarding the perinatal factors study (Study III), the exclusion of multiple births due to known Medical Birth Register data quality issues for these pregnancies (mentioned in Study III Methods section regarding excluded observations) is appropriate but limits generalizability to singleton pregnancies only. The mediation analysis, while providing valuable insights into potential pathways, relies on assumptions including no unmeasured confounding of the exposure-mediator, mediator-outcome, and exposure-outcome relationships, which cannot be fully verified in observational data.

For the pregnancy outcomes study (Study IV), unmeasured factors such as access to prenatal care, experiences of discrimination in healthcare settings, social support, and mental health during pregnancy could influence outcomes but were not available in register data. The categorization of cohorts based on timing relative to diagnosis and testosterone treatment provides temporal information but may not fully capture the complexity of individual reproductive and transition timelines.

Despite these limitations, the studies provide new insights on questions in GD research and clinical care. The consistency of findings across multiple studies with complementary designs strengthens the overall conclusions.

Future Research Directions

The findings from these four studies point to several directions for future research. First, the intrauterine hypothesis suggested by Study I warrants further investigation. This should involve the use of cohorts with confirmed zygosity information, assessment of intrauterine exposures that are unique to different-sex twin pregnancies where feasible, and examination of other twin-specific exposures that might influence gender identity development. Second, the neurodevelopmental pathway identified in Study III warrants exploration through prospective studies examining trajectories from perinatal exposures through early neurodevelopment to gender identity outcomes.

Third, regarding treatment safety, larger international collaborations could provide sufficient power to detect rare adverse events associated with GnRHa treatment and to compare safety profiles across different pharmaceutical formulations. Long-term follow-up studies examining diverse health outcomes beyond IIH would further inform evidence-based clinical guidelines.

Fourth, pregnancy and reproductive health research in TGD populations requires expansion beyond single-country studies to examine how different healthcare systems, legal frameworks, and social contexts influence pregnancy outcomes. Prospective cohort studies collecting detailed information on prenatal care experiences, testosterone regimens, mental health, social support, and discrimination would provide more nuanced understanding of factors influencing pregnancy outcomes. Research is also needed on reproductive counseling, fertility preservation, and family-building experiences in TGD individuals.

Significance

This thesis addresses key questions about gender dysphoria in three areas: potential etiological pathways, selected treatment safety outcomes, and pregnancy outcomes in transgender and gender diverse populations.

Study I provides evidence suggesting that intrauterine environmental factors, rather than solely genetic or shared childhood environmental influences, may play a significant role in GD development. The striking difference in concordance between different-sex twins and both same-sex twins and non-twin siblings challenges prevailing assumptions about the heritability of clinically diagnosed GD and suggests important directions for etiological research focused on prenatal developmental periods.

Study II addresses a timely clinical safety question, providing reassuring evidence that does not support a substantial association between GnRHa treatment and IIH in individuals with GD. These findings are directly relevant to clinical decision-making and informed consent discussions, particularly in the context of recent regulatory warnings that may have caused concern among patients, families, and healthcare providers.

Study III advances understanding of potential neurodevelopmental pathways to GD by demonstrating that ASD fully mediates associations between several perinatal factors and GD. This finding has implications for understanding the co-occurrence of GD and neurodevelopmental conditions, suggesting shared developmental vulnerabilities that may inform both clinical assessment and support services. The high prevalence of ASD among individuals with GD underscores the importance of neurodevelopmental considerations in clinical care for this population.

Study IV provides much-needed evidence on pregnancy outcomes in TGD individuals from a European context, expanding beyond the predominantly US-based literature. The findings indicate patterns of socioeconomic vulnerability in the pre-diagnosis period, comparable outcomes post-diagnosis for most measures, and preliminary evidence suggesting no major adverse effects of testosterone on birth outcomes in a small sample. These findings inform clinical counseling, highlight the importance of addressing social determinants of health in TGD populations, and identify areas where additional healthcare support may be beneficial.

Collectively, the four studies demonstrate the value of population-based register research for addressing diverse questions in gender dysphoria research, from etiology to treatment safety and pregnancy outcomes. The findings support a view of GD development as multifactorial, suggest that gender-affirming treatments are generally safe within the contexts studied, and point to heterogeneous healthcare needs in childbearing TGD populations. By adding data in areas where evidence has been limited, this work may inform clinical practice, policy discussions, and future research.

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