

**EXHIBIT 24**

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**Subject:** FW: [EXT] Fwd: FW: attachments  
**Attachments:** witches mpd.pdf; Hayes Directory.pdf; 20170619\_TNA52HruzMayerMcHugh.pdf; Long-Term Follow-Up of Transsexual Persons - Sweden.pdf

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**From:** Paul McHugh  
**Sent:** Monday, February 5, 2018 2:51 PM  
**To:** '[william.bushman@sd.mil](mailto:william.bushman@sd.mil)' <[william.bushman@sd.mil](mailto:william.bushman@sd.mil)>  
**Subject:** attachments

Mr. Bushman, I mentioned these several articles in our conversation The Hayes Directory on evidence for sex reassignment surgery and other medical treatments , The long term follow-up from Sweden for transgender surgery, My article in Nature Medicine in 1995, and our recent article in the New Atlantis. I've attached them all here . Do tell me if they get through. Paul McHugh

# Witches, multiple personalities, and other psychiatric artifacts

Contemporary psychiatric misdirections derived primarily from standard medical errors of oversimplification, misplaced emphasis, and invention are reviewed. These particular errors, however, were in part prompted and sustained by the sociocultural fads and fashions of the day. The results have been disastrous for everyone — patients, families, the public and psychiatry itself.

PAUL R. McHUGH

Psychiatry is a medical discipline long on disorders and short on explanations. Just a glance at the *Diagnostic and Statistical Manual* now in its fourth edition (DSM-IV) will confirm this verdict. DSM-IV presents hundreds of psychiatric disorders arranged according to their symptoms—depression, anxiety, schizophrenia and the like—but quite scrupulously avoids an etiological arrangement. Its authors are aware that psychiatrists tend to split up into camps, based on purported explanation — hence, biological, dynamic, behavioural, and even the eclectic — and go to war with one another.

However, this shortage of agreed-upon explanations brings good news and bad news. The good news is there is plenty of room for useful scientific research in psychiatry and a great deal of this is going on at the moment! The bad news is, because practitioners in this discipline are hungry for explanations today, at least once each decade, psychiatry is swept by an enthusiasm for a fundamentally incoherent practice, and then must spend at least ten years subsequently digging out of the troubles that this practice produced. These misdirections of psychiatry rest squarely on standard medical mistakes such as oversimplification, misplaced emphasis or pure invention. The enthusiasms for these misdirections, however, usually derive from an uncritical acceptance of transient cultural attitudes and fashionable ideas. The repeated combination of these elements proves how all too often the discipline of psychiatry has been the captive of culture, to the detriment of everyone.

## Anti-psychiatry

The most conspicuous misdirection of psychiatric practice — the precipitate dismissal of patients with severe, chronic mental disorders such as schizophrenia, from psychiatric hospitals — required a vastly oversimplified view of mental illness. Ironically, these actions were defended as efforts to bring 'freedom' to

these people, sounding a typical 1960s cultural theme that marched right by the fact that it was the patients' illnesses that had deprived them of freedom in the first place. There were several collaborators in this sad enterprise. Prominent among them were state governments looking for release from the traditional but heavy fiscal burden of housing the mentally ill. Crucial to the process was the combination of fashionable opinions of the era about society's institutions as oppressive and oversimplified explanatory opinions about schizophrenia and other mental illnesses generated by the so-called anti-psychiatrists, Thomas Szasz, R.D. Laing, Erving Goffman, and Michel Foucault, notably among them.

A simple description of the mental problems of psychiatric patients was not the style of our 1960s commentators. They were more interested in painting a picture of their own devising. A picture that would provoke first suspicion and then disdain for contemporary psychiatric practices. And it did so, not by producing new standards or reforming specific practices, but by ridiculing and caricaturing efforts of the doctors and the institutions, just as fashion directed. The power of scorn was surprising and had amazing results, leading many in the public and not a few in the profession to believe that it was the institutions that provoked the patients' troubles rather than illness that called out for shelter and treatment. Here from Szasz's book, *Schizophrenia — The Sacred Symbol of Psychiatry*<sup>2</sup>, is a typical comment: "The sense in which I mean that Psychiatry creates schizophrenia is readily illustrated by the analogy between institutional psychiatry and involuntary servitude. If there is no slavery there can be no slaves . . . Similarly if there is no psychiatry there can be no schizophrenics. In other words, the identity of an individual as a

schizophrenic depends on the existence of the social system of (institutional) psychiatry."

Effective replies to such commentary demanded knowledge first of the patients themselves, in schizophrenia, people impaired by delusions, hallucinations and disruptions of thinking capacities, but also understanding of how the concept of disease has, essentially since Sydenham, provided physicians with a coherent, logical, and stepwise approach to human afflictions, from symptom clusters to etiology, ultimately. The disparagement of this approach by the likes of Szasz demonstrated an ignorance of the explanatory potential of the concept of disease right from the start.

A saving grace for any medical theory or practice (the thing that spares it perpetual thralldom to the gusty winds of fashion) is the patients. They are real, they are around and a knowledge of their distressing symptoms guards against oversimplification. The claim that schizophrenic patients are in any sense living an alternative life style that our institutions were inhibiting was fatuous. Every urban citizen now recognizes, because of a familiarity with the many homeless people that the anti-psychiatric fad generated, that these patients have impaired capacities to comprehend the world and that they need protection and serious active treatment.

As well, and fortunately, the enterprises of brain research launched subsequent to these pronouncements have documented a cerebral source for many of the particular symptoms of schizophrenia<sup>3,4</sup>. This research tends to confirm that the conceptual model of epilepsy that helped sort out that condition (distinguishing symptomatic epilepsies, caused by some coarse brain pathology, from the idiopathic epilepsies, that rest upon genes) also makes sense of the group of conditions called schizophrenia<sup>5</sup>. The ultimate solutions for the homeless mentally ill are still to

be found but, as the saying goes, the anti-psychiatrists are history.

### A question of gender

A similar combination of a cultural fad amidst a dearth of explanations led to the grim practice of sex reassignment surgery in the 1970s. I happen to know about this because Johns Hopkins was one of the places in the United States where this practice, with what at the time were called transsexuals, was given its start.

Typically a man comes to the clinic and says something like, "As long as I can remember, I've thought I was in the wrong body. True, I've married and had a couple of kids but always, in the back and now more often in the front of my mind, there's this idea that actually I'm more a woman than a man. I'm here because all this male equipment is disgusting to me. I want medical help to change my body: hormone treatments, silicone implants, surgical amputation of my genitalia and the construction of a vagina. Will you do it?"

The patient claims it is a torture for him to live as a man, especially now that he has read in the newspapers about the possibility of switching surgically to womanhood. Upon examination it is not difficult to identify other mental and personality difficulties in him, but he is primarily disquieted because of his intrusive thoughts that his sex is not a settled issue in his life.

The skills of our plastic surgeons, particularly on the genitourinary system, are impressive. They were obtained, however, not to treat a presumptive gender identity problem but to repair congenital defects, injuries and the effects of destructive diseases such as cancer in this region of the body. That you can get something done doesn't always mean that you should do it. There are so many problems right at the start. In sex reassignment cases, the patient's claim that this has been a lifelong problem is seldom checked with others who have known him since childhood. It seems so intrusive and untrusting to discuss the problem with others even though they might provide a better gauge of the seriousness of the problem, how it emerged, its fluctuations of intensity over time and its connection with other experiences.

When you discuss what the patient means by "feeling like a woman," you often get a sex stereotype in return and something that female physicians note immediately as a male caricature of women's attitudes and interests. One of our patients, for example, said that, as a woman, he would be more "invested with being than with doing."

Experts say that a sense of one's own maleness or femaleness rests upon a complicated biopsychological process and suggest that some derangement in this

***. . . psychiatrists do not understand what is the problem here but hope surgery may do the poor wretch some good.***

natural process may be the explanation for this problem. They venture that, although their research on those born with genital and hormonal abnormalities may not apply to a person with normal bodily structures, something must have gone wrong in this patient's early and formative life to cause him to feel as he does. Why not help him look more like what he says he feels? Our surgeons can do it.

On the other hand it is not obvious how this patient's sense that he is a woman trapped in a man's body differs from the feelings of a patient with anorexia nervosa that she is obese despite her emaciated, cachectic state. We don't do liposuction on anorexics. So why amputate the genitals of these patients? Surely, the fault is in the mind, not the member.

A plastic surgeon at Hopkins provided the voice of reality on this matter based on his practice and his natural awe at the mystery of the body. One day while we were talking about it, he said to me: "Imagine what it's like to get up at dawn and think about spending the day slashing with a knife at perfectly well formed organs, because you psychiatrists do not understand what is the problem here but hope surgery may do the poor wretch some good."

The zeal for this sex change surgery did not derive from critical reasoning or thoughtful assessments. The energy came from the fashions of the 1970s that invaded the clinic. If you can do it and he wants it, do it. This fashion was integral to an aesthetic that saw diversity as everything, and could accept any idea, including that of surgical sex change, as interesting, and resistance to such ideas as uptight or even oppressive. Yet, moral matters should have some salience here.

These include the confusions imposed on society where these men/women insist on acceptance even in athletic competition with women; the encouragement of the 'illusion of technique' which assumes that the body is like a suit of clothes to be hemmed and stitched to style; there is the ghastliness of the mutilated anatomy to consider; and finally, consider that this surgical practice has distracted effort from genuine investigations attempting to find out just what has gone wrong for these people. What has, by their testimony, given them years of torment and psychological distress and prompted them to accept these grim and disfiguring surgical procedures.

We now appreciate that this condition falls into the category of "overvalued ideas"<sup>6</sup> described very thoroughly by Carl Wernicke<sup>7</sup> at the beginning of the century. This is a category that includes morbid jealousies, anorexia nervosa and litigious personalities. Fortunately the diagnostic term transsexualism has been abandoned and replaced with the term Gender Identity Disorder making it clear that the problem is one of ideas rather than of bodily constitution and should be treated as such.

Psychiatrists collaborated in an exercise of folly with distressed people, and a misplaced emphasis proved hazardous when explanations were at a premium.

### Artifactual behaviour

Medical errors of oversimplification and misplaced emphasis usually play themselves out with consequences all can see. Pure inventions can bring out a darker, hateful potential when psychiatric thought goes awry in search for an explanation. Most psychiatric histories choose to describe such invention by detailing its most vivid example — witches. The experience in Salem, Massachusetts, of 300 years ago is prototypical<sup>8</sup>.

Briefly, in 1692, several young women and girls who had for some weeks been secretly listening to tales of spells, voodoo, and illicit cultic practices from a Barbados slave suddenly displayed a set of mystifying mental and behavioural changes. They developed trance-like states, falling on the ground and flailing, and screaming at night and at prayer, seemingly in great distress and in need of help. The local physician, who witnessed this, was as bewildered as anyone else and eventually made a diagnosis of "bewitchment". "The

evil hand is on them", he said and turned them over to the local law officials for examination and ultimately for protection. The clergy and magistrates assumed, taking their lead from the doctor, that local agents of Satan were at work and, using as grounds the answers of these young women to leading questions, indicted several citizens for bewitching them. The accepted proof of guilt was bizarre. The young women spoke of ghostly visitations by the defendants to their homes to torment them, all occurring while the accused were known by the testimony of reliable witnesses to be elsewhere. The victims often screeched out in court that they felt the accused pinching them even as everyone could see the defendants sitting quietly on the other side of the court room. Strange as it seems this testimony had great weight because the judges and the juries believed that capacities of this kind — provoking injury from a distance or being in two places at the same time — were skills and powers of witches. On the basis of this "spectral" evidence they dismissed all protests of innocence by the defendants and promptly executed them. The whole exercise should have been discredited when, after the executions, there was no change in the distraught behaviour of the young women. Instead more and more citizens were indicted. Eventually, good sense began to prevail, in part because many citizens came to recognize that no one was safe against these accusations and in part because a prosecution depending on spectral evidence was recognized to be as irrefutable as it was undemonstrable. The trials ceased and ultimately several of the young women admitted that their beliefs had been "delusions" and their accusations false.

The proper psychiatric diagnosis for those young women is, of course, not bewitchment but any of a series of terms such as hysteria, factitious disorder or malingering, all attempting to communicate the view that the mental states and behaviours of these individuals should be recognized as artifacts. A psychiatric or psychological artifact, like a physical artifact, is a product of human crafting. It is not a product of nature, such as a disease, but something manufactured by some person or persons for some human purpose or action. Behavioural displays in

which physical or mental disorders are imitated (artifactual clinical disorders) are common enough on any medical service. On inspection, the patient's manufactured imitations of illness derive from a variety of different sources of information and suggestion, and they serve a variety of personal goals. In this era artifactual clinical conditions usually represent an effort on the part of a troubled person to take on the sick role with the benefits of care, attention and support this status brings to an individual. The status of 'bewitched' in Salem of 1692 brought both attentive concern and the license to indict any enemy to young women previously scarcely noticed by the community.

Forms of artifactual behaviour whether they are physical activities, such as falling and shaking, or mental phenomena, such as pains, visions or memories are partially shaped by unintended suggestions from others and sustained by the attention of onlookers and especially onlookers such as doctors who are socially empowered to assign, by affixing a diagnosis, the status of patient to a person. Whenever a diagnostician mistakes an artifact for what it is attempting to imitate by misidentifying the artifact either as some natural process, such as epilepsy, or inventing some specious explanation for it, such as bewitchment, then the behavioural display will continue, expand, prove treatment resistant and, in certain settings, spread to others. The usual result is trouble. Over the last decade a remarkable example of manufactured artifactual behaviour has surfaced and has been misidentified and bolstered by an invented view of its cause that fits a cultural fashion. This condition is Multiple Personality Disorder (MPD).

### Multiple personality disorder

Patients who are eventually diagnosed as suffering from MPD come to therapists with standard psychiatric complaints such as depression or anxiety. Some therapists see much more in these symptoms and suggest to the patient, and to others, that the symptoms represent the subtle actions of several alternative personalities, alters, coexisting in the patient's mental life. These suggestions encourage many patients to see their problems in a new light. Suddenly they are transformed

into odd people with repeated shifts of demeanor and deportment that they display on command and sometimes in response to hand signals from the therapist. An artifactual behaviour has been generated by the combination of the vulnerabilities of the patient to suggestion and the beliefs of the therapists.

Sexual politics in the 1980s and 1990s, particularly about sexual oppression and victimization, galvanizes these inventions. Forgotten (repressed) sexual mistreatment is the proffered explanation of MPD. Just as an epidemic of bewitchment served to prove the arrival of Satan in Salem, so in our day an epidemic of MPD is used to propose that a vast number of adults were sexually abused by guardians during their childhood, the MPD being one of the presumed expressions of the traumatic experience. Now, I do not for a moment deny that children are sometimes victims of sexual abuse or that such abuse would produce psychiatric symptoms. Such realities are not at issue. What I am concerned with here is what has been imagined from these realities and inventively applied.

Adults with MPD, so theory goes, were assaulted as young children by a trusted and beloved person, usually a father although grandfathers, uncles, brothers, or others, often abetted by women in their power, are also possibilities. This sexual assault, the theory holds, is blocked from memory (repressed and dissociated) because it was so shocking. This dissociating blockade itself is purported to destroy the integration of

*Today's awful version of psychiatric invention is the notion that many people suffered sexual abuse — if only they remembered.*

mind and evokes multiple personalities as separate, disconnected, sequestered, 'alternative' collections of thought, memory and feeling. These resultant distinct 'personalities' produce a variety of what might seem standard psychiatric symptoms, such as depression, weight problems, panic states or demoralization, that only careful review, by experts on psychic life, will reveal to be expressions of MPD and the outcome of sexual abuse.

These patients have not come to treatment reporting a sexual assault in childhood. Only as the therapy is developed is the possibility that they were sexually abused as children suggested to them. From recollections of the mists of childhood, a vague sense of vulnerability may

slowly emerge, facilitated and encouraged by the treating group. This sense of vulnerability is thought a harbinger of clearer memories of victimization that, although buried, have been active for decades producing the different 'personalities'. The long 'forgotten' abuse is finally 'remembered' after sessions of 'uncovering' therapy, during which long conversations take place, often enhanced by sodium amytal or by hypnotic inductions, between the therapist and alter personalities, personalities that usually will be of all age ranges, differing sexes and not uncommonly animals that must also be made to speak.

Any actual proof of the provocative sexual assault is thought unnecessary since the presence of the MPD is thought proof enough. Theory about how the mind works and how its manifestations are to be understood is considered quite adequate to accuse the patient's parents of vile and atrocious acts against the patient when she (some 85% are women) was a child, with nothing more than this new form of spectral evidence, evidence that is just as irrefutable as that at Salem.

The idea of MPD and its cause has caught on among large numbers of psychotherapists. Its partisans see the patients as victims, cosset them in groups, encourage more expressions of alters (up to as many as 100 or more), and are ferocious towards any defenders of the perpetrators of the abuse. Just as the divines of Massachusetts were convinced that they were fighting Satan by recognizing bewitchment, so the contemporary divines, these therapists, are confident that they are fighting sexual oppression and child abuse, by recognizing MPD. The incidence of MPD has of late taken on epidemic proportions particularly in certain treatment centers. Whereas its diagnosis was reported less than 200 times from a variety of supposed causes prior to 1970, it has been applied to more than 20,000 people in the last decade and largely attributed to sexual abuse.

I have been involved, either directly or indirectly, with more than thirty such cases in the last few years. In every one, the very same story has been played out in a stereotyped script-like way. In each, a young woman with a rather straightforward set of psychiatric symptoms (depression and demoralization) sought psychotherapeutic help and her case was stretched during a course of therapy into a diagnosis of repressed memories of sex-

ual abuse, a delayed form of Post Traumatic Stress Disorder and usually MPD. In each case, an accusation of prior sexual abuse was levelled by her, usually against her father but in about thirty percent of cases against the mother. The accusation developed, always after the onset of therapy, first as vague feelings of dream-like childhood reminiscences of danger and darkness and eventually crystallizing, sometimes in a flash, into a rec-

ollection of father forcing sex upon the patient as a child. No other evidence of these events was presented. Refuting testimony, coming from former nursemaids or the other parent for example, was dismissed if presented.

On one occasion, the identity of the molester changed. This change was as telling about the nature of evidence as was the emergence of the original charge. A woman called her mother to

IMAGE  
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The Salem witch trial

Bettmann Archives

claim that she had come to realize that when she was young she was severely and repeatedly sexually molested by a maternal uncle. The mother questioned the daughter about the dates and times of these incidents to determine if they were even possible. She soon discovered that her brother was on military service in Korea at the time of the alleged abuse and with this information, the mother went to her daughter with the hope of showing her that her therapist was misleading her in destructive ways. When she heard this new information, the daughter seemed momentarily taken aback, but then said, "I see, Mother. Yes. Well, let me think. If your dates are right, I suppose it must have been Dad." And with that, she began to claim that she had been a victim of her father's abusive attentions and nothing could dissuade her.

The accused parents whom I studied, denying the charges and amazed at their source, submitted to detailed reviews of their sexual lives and any other efforts up to and including polygraphic testing to try to prove their innocence. Professional requests by me to the daughters' therapists for better evidence of the abuse were dismissed as derived from the pleadings of the guilty and were deemed beneath contempt given that the diagnosis of MPD indicated, and the ultimate testimony of the patient's patently confirmed, the sex abuse.

### Remembered trauma

In Salem, the convictions of the defendants depended on how judges thought witches behaved. In our day, similar convictions depend on how some therapists think memory of trauma customarily works. In fact, standard psychiatric teaching in the past held that severe traumas are usually remembered all too well. They are amplified in consciousness, remaining like grief to be reborn and re-emphasized on anniversaries and in settings that can simulate the environments where they occurred. Good evidence for this was found in the memories of children from concentration camps. More recently, the children of Chowchilla, California, who were kidnapped in their school bus and buried in sand for many hours, remembered every detail of their traumatic experience years later and needed psychiatric assistance, not to bring out forgotten material that was repressed but to help them move away from a constant ruminative preoccupation with the experience<sup>9</sup>.

Many psychiatrists upon first hearing of these diagnostic formulations (MPD being a form of post traumatic stress and the result of repressed memories of sexual abuse in childhood) have fallen back upon what they think is an even-handed way of approaching it. The mind is very mysterious in its ways, they say, anything is possible in a family. In fact, this credulous stance towards evidence and the failure to consider the alternative of artifactual behaviours, memories and beliefs continue to support this crude psychiatric analysis, and if the kinds of practices that lie behind the diagnosis of MPD become standard in psychiatry, then no family with a member in psychotherapy is safe from a persecution galvanized by the same kind of energy and reasoning that launched the witches' court or the lynch mob.

The helpful clinical approach to the patient with putative MPD, as with any instance of an artifactual display, is to direct attention away from the manufactured behaviour — one simply never talks to an alter. Within a few days of a consistent therapeutic focus away from the MPD behaviour and on to the issues of depression and anxiety that were the presenting matters, preoccupations with alters and supposed repressed memories fade and generally useful psychotherapy begins.

This epidemic will end in the same way that the witch craze ended in Salem. The MPD phenomena will be seen as manufactured, the 'repressed memory' explanations will be recognized as misguided, and psychiatrists will become immunized against the practices that generated these artifacts<sup>10</sup>. Meanwhile, time is passing, many families are being hurt and confidence in the competence and impartiality of psychiatry is eroding.

### A time to learn

Major psychiatric misdirections often share this intimidating mixture of a medical mistake and a trendy idea. Any challenge to such a misdirection must confront simultaneously the professional authority of the proponents and the political power of fashionable convictions. Such challenges are not for the faint-hearted or inexperienced. They seldom quickly succeed because they are often misrepresented as ignorant or, in the cant word of our day, uncaring.

In ten years much damage can be done, and much effort over a longer period of time is required to repair it. Thus

with the mentally ill homeless, only a new crusade and social commitment will bring them adequate psychiatric services again. Age increases the sad caricature of the sexual reassigned and saps their bravado. Some, pathetically, even ask about re-assignment. And groups of parents falsely accused of sexual mistreatment by their grown children are gathering together to fight back against psychotherapists in ways that are producing dramatic but distressing court room spectacles. How good it would have been if all these misguided programs had been avoided or at least their span abbreviated.

Psychiatry is a medical discipline. It is capable of medical triumphs and serious medical mistakes. We don't know the secret of human nature. We cannot build the New Jerusalem. We can describe how our explanations for mental disorders are devised and develop, and where they are strong and where they are limited. We can clarify the presumptions about what we know and how we know it. With more research, steadily, we can construct a clinical discipline that, while delivering less to fashion, will bring more to patients and their families.

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A prior version of this essay appeared entitled "Psychiatric Misadventures" in *The American Scholar*, 61, 497–510, (1992).

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Hayes directory

May 15, 2014

## Sex Reassignment Surgery for the Treatment of Gender Dysphoria

### PURPOSE OF TECHNOLOGY:

Sex reassignment surgery (SRS), which involves genital reconstruction surgery and chest surgery, is part of the treatment approach for persons with gender dysphoria (GD). Individuals with GD have persistent feelings of gender discomfort and inappropriateness of their anatomical sex, strong and ongoing cross-gender identification, and a desire to live and be accepted as a member of the opposite sex. SRS includes the surgical procedures by which the physical appearance and function of a person's existing sexual characteristics are changed to those of the other sex in an effort to resolve or minimize GD and improve quality of life.

### EXECUTIVE SUMMARY:

**Health Problem:** People with gender dysphoria (GD) feel a severe incongruity between anatomical sex and gender identity. The prevalence of GD is 1 in 11,900 to 1 in 45,000 persons for male-to-female (MtF) and 1 in 30,400 to 1 in 200,000 persons for female-to-male (FtM) transgender persons.

The earlier term, *gender identity disorder* (GID), has given way to *gender dysphoria* (GD). This change was intended to reflect a consensus that gender nonconformity is not a psychiatric disorder, as it was previously categorized. However, since the condition may cause clinically significant distress and since a diagnosis is necessary for access to medical treatment, the new term was proposed. The diagnostic criteria for GD outlined in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), as well as the criteria for GID in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV), require that the individual believes there is a marked difference between the gender assigned to him or her by others and the gender he or she experiences or wishes to express. Additional criteria must also be met for a diagnosis of GD.

**Determinants:** The determinants of GD are poorly understood. Experts believe that gender identity develops as the result of a combination of biological factors, possibly including genetic and/or prenatal and perinatal hormonal influences, and environmental influences that have psychological effects.

**Treatment:** Individuals with GD seeking professional help begin with psychotherapy. An American Psychiatric Association Task Force recommends 2 goals for psychotherapy: (1) to explore issues related to the individual's commitment to living in the cross-gender role; and (2) to fully explore other options for the patient including whether to live as a homosexual person without medical and surgical treatments for gender transition.

The full therapeutic approach to GD consists of 3 elements or phases, typically in the following order: (1) hormones of the desired gender, (2) real-life experience for 12 months in the desired role; and (3) surgery to change the genitalia and other sex characteristics (e.g., breast reconstruction or mastectomy). However, not everyone with GD needs or wants all elements of this triadic approach.

**Technology:** Sex reassignment surgery SRS involves modification of the genitalia and/or breast/chest to resemble that of the opposite sex.

For the FtM patient, surgical procedures may include mastectomy, hysterectomy, salpingo-oophorectomy, vaginectomy, metoidioplasty, scrotoplasty, urethroplasty, placement of testicular prostheses, and phalloplasty.

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## Sex Reassignment Surgery for GD

For the MtF patient, surgical procedures may include breast augmentation, penectomy, orchiectomy, vaginoplasty, clitoroplasty, and labiaplasty.

**Rationale:** The goal of SRS is to feminize or masculinize the body to facilitate an individual's desire to live in the gender role opposite from the biological sex.

**Controversy:** The medical necessity of SRS for the treatment of GD is under debate. The condition does not readily fit traditional concepts of medical necessity since research to date has not established anatomical or physiological anomalies associated with GD. An evidence-based assessment of the effectiveness of SRS procedures for alleviation of symptoms associated with GD and improvement of recipients' well-being can make a helpful contribution to this controversy.

### Relevant Questions:

- Has SRS been shown to be effective in improving patient-important outcomes such as relief of symptoms of GD, quality of life (QOL), satisfaction with sex characteristics, psychological well being, or sexual function?
- Does SRS confer additional benefits to hormone therapy alone?
- Do outcomes vary according to which components of SRS are performed?
- Is SRS safe?
- Have definitive patient selection criteria been established for SRS as treatment for GD?

**Evidence Base:** Nineteen peer-reviewed studies, primarily case series, cross-sectional studies or pretest-posttest studies assessing the effectiveness of SRS were analyzed in this report. In addition, 6 case series evaluating safety outcomes in  $\geq 300$  MtF patients or  $\geq 200$  FtM patients following SRS were analyzed.

**Search Dates:** November 2004 to April 2014.

**Sample Sizes:** 35 to 376 patients for main evidence review, 202-390 patients for safety evidence.

**Patients:** MtF patients (6 studies), FtM patients (6 studies), both MtF and FtM patients (7 studies).

**Interventions:** Chest surgery only (5 studies), genital surgery only (5 studies), both chest and genital surgery (4 studies), unspecified (5 studies).

**Comparisons:** Transgendered patients that had undergone SRS vs. those that had not undergone SRS (5 studies) and outcomes in SRS patients that were MtF vs. FtM (1 study).

**Outcome Measures:** GD, QOL, sexual experience, patient satisfaction, psychological outcomes, and safety outcomes.

**Follow-Up:** 1 month to 7 years.

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**Hayes**

Transforming Healthcare with Evidence

MCHUGH 00008

## Sex Reassignment Surgery for GD

**Findings:** Following SRS, patients reported decreased GD, depression and anxiety, and increased QOL. The majority of SRS patients were sexually active, but the ability to orgasm varied across studies. The majority of patients were satisfied with their aesthetic results following SRS.

**Gender Dysphoria:** GD was decreased following SRS relative to baseline (2 studies).

**Quality of Life:** Transgendered patients who underwent SRS had improved QOL relative to patients that had not undergone SRS (1 study), improved QOL relative to before SRS (2 of 3 studies), and had QOL scores similar to those of the general population (2 studies).

**Sexual Function:** The majority of patients were sexually active following SRS (4 studies), and the ability to orgasm varied across studies (5 studies).

**Patient Satisfaction:** The majority of patients were satisfied with aesthetic results following SRS (10 studies).

**Psychological Outcomes:** Depression (3 studies) and anxiety (2 studies) decreased following SRS.

**Other Outcomes:** Following SRS, almost all FtM patients were able to micturate while standing (1 study), and rates of employment were high (3 studies).

**Comparative Effectiveness of Hormone Therapy Alone and SRS:** The evidence was too sparse to allow any conclusion regarding the comparative benefits of SRS and hormone therapy alone.

**Comparative Effectiveness of Different Types of SRS:** The evidence was too sparse to allow any conclusion regarding the comparative benefits of different SRS procedures.

**Safety:** Following SRS, there were very low rates of regret of surgery (0% to 6%) (5 studies) and suicide (2 to 3%) (3 studies). Only 6 of the 19 studies reported on complications following SRS, and the most common complications were urinary tract complications (4% to 33%) (3 studies), necrosis of tissue (1% to 10%) (6 studies), vaginal stenosis or prolapse (2% to 14%) (3 studies), and need for revision surgery (4% to 29%) (3 studies). The most common complications reported in the 6 safety studies were need for revision surgery (22% to 40%) (5 studies), urinary tract complications (40% to 41%) (2 studies), and wound healing difficulties (11% to 33%) (2 studies). The majority of studies reported a length of follow-up of at least 1 year following surgery (12 studies).

**Patient Selection Criteria:** There is insufficient evidence to establish patient selection criteria for SRS to treat GD. Professional groups recommend that SRS be restricted to individuals who are referred for sex reassignment services by a qualified mental health professional, and that while 1 referral is sufficient for breast or chest surgery, 2 independent referrals should be required for genital SRS. Individuals who have medical contraindications to surgery should not undergo SRS.

**Quality of Evidence:** Very low.

Overall, the quality of the evidence was very low due to limitations of individual studies, including small sample sizes, few studies evaluating any 1 outcome, retrospective data, lack of randomization of patients to treatment groups, failure to blind outcome assessors to group assignment, lack of a control or comparator group or

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## Sex Reassignment Surgery for GD

minimal adjustment for confounders, lack of baseline assessments to assess change over time, a possible procedural learning curve, and a lack of objective and validated outcome measures.

**Conclusions:** The evidence suggests positive benefits but because of serious limitations permit only weak conclusions regarding sex reassignment surgery (SRS) for gender dysphoria (GD). No conclusions can be made about the comparative benefits of hormone therapy alone and SRS, or about different components of SRS.

- Patients who underwent chest/breast or genital surgery were generally pleased with the aesthetic results.
- Following SRS, patients reported decreased GD, depression and anxiety, and increased quality of life.
- The majority of SRS patients were sexually active, but the ability to orgasm varied across studies.
- Complications of surgery following SRS were common and could be serious.
- Rates of regret of surgery and suicide were very low following SRS.
- Data were too sparse to draw conclusions regarding whether SRS conferred additional benefits to hormone therapy alone.
- Data were too sparse to draw conclusions regarding whether outcomes vary according to which surgeries were performed.

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### Hayes Rating:

- C - For sex reassignment surgery (SRS) to treat gender dysphoria (GD) in adults for whom a qualified mental health professional has made a formal diagnosis of GD, have undergone hormone therapy and psychotherapy, and have undergone a "real-life" test (i.e., in which they lived as the desired gender role). This Rating reflects the reporting of some positive evidence but serious limitations in the evidence of both effectiveness and safety.
- D2 - For SRS to treat GD in adolescents. This rating reflects the paucity of data of SRS in adolescents.

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### INSIGHTS:

- Since part of the reason for the psychopathology experienced by transgender persons has to do with the reactions or expected reactions of family and society, evolving social norms theoretically could diminish the perceived need to undergo physical changes in order to live in the desired gender role.
- The majority of the studies selected for this report reflect the diagnostic criteria of *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, rather than the somewhat expanded criteria published in 2013 in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*.

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**Hayes**

Transforming Healthcare with Evidence

MCHUGH 00010

May 19, 2014

## Hormone Therapy for the Treatment of Gender Dysphoria

### PURPOSE OF TECHNOLOGY:

Continuous feminizing or masculinizing hormone therapy is administered to some adolescents and adults who have a diagnosis of gender identity disorder (GID) or gender dysphoria (GD). The purpose of this therapy is to facilitate a transgender individual's desire to transition to a sexual identity other than his or her biological (natal) sex. Some individuals undergo hormone therapy as a prelude to sex reassignment surgery; other individuals seeking gender transition undergo hormone therapy without ever undergoing any type of surgery.

### EXECUTIVE SUMMARY:

**Health Problem:** Individuals with gender dysphoria (GD) experience a severe incongruity between their biological sex and gender identity.

The prevalence of transsexualism is estimated to be 1 in 11,900 to 1 in 45,000 persons for male-to-female (MtF) prevalence and 1 in 30,400 to 1 in 200,000 for female-to-male (FtM) prevalence. The prevalence of gender dysphoria within the transsexual population is unknown. The earlier term, *gender identity disorder* (GID), has given way to *gender dysphoria* (GD). This change was intended to reflect a consensus that gender nonconformity is not a psychiatric disorder, as it was previously categorized. However, since the condition may cause clinically significant distress and since a diagnosis is necessary for access to medical treatment, the new term was proposed. The diagnostic criteria for GD outlined in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), as well as the criteria for GID in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV), require that the individual believes there is a marked difference between the gender assigned to him or her by others and the gender he or she experiences or wishes to express. Additional criteria must also be met for a diagnosis of GD.

**Determinants:** The determinants of gender dysphoria are poorly understood. Experts believe that gender identity develops as the result of a combination of biological factors, possibly including genetic and/or prenatal and perinatal hormonal influences, and environmental influences that have psychological effects.

**Treatment:** Individuals with GD seeking professional help begin with psychotherapy. An American Psychiatric Association Task Force recommends 2 goals for psychotherapy: (1) to explore issues related to the individual's commitment to living in the cross-gender role; and (2) to fully explore other options for the patient, including whether to live as a homosexual person without medical and surgical treatments for gender transition. The full therapeutic approach to GD consists of 3 elements or phases, typically in the following order: (1) hormones of the desired gender; (2) real-life experience for 12 months in the desired role; and (3) surgery to change the genitalia and other sex characteristics (e.g., breast reconstruction or mastectomy). However, not everyone with GD needs or wants all elements of this triadic approach.

**Technology:** The goal of cross-sex hormone therapy for GD is to alter secondary sex characteristics, including such features as fat distribution, hair growth, voice pitch, and muscle strength.

Cross-sex hormone therapy includes estrogens and testosterone-blocking agents administered to natal (biologic) males and androgens (usually testosterone) administered to natal females. Adolescents with a

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## Hormone-GD

diagnosis of GD may be eligible for puberty-delaying hormones as soon as pubertal changes begin; the effects of this treatment are fully reversible.

**Rationale:** Hormone therapy serves to feminize or masculinize the body to facilitate an individual's desire to live in the gender role opposite from biological sex.

**Controversy:** Numerous professional groups have advocated for third-party payers to cover all medically necessary treatments to alleviate GD. However, the condition does not readily fit traditional concepts of medical necessity since research to date has not established anatomical or physiological anomalies associated with GD.

An evidence-based assessment of the effectiveness of hormone therapy for alleviation of symptoms associated with GD and improvement of recipients' well being can make a helpful contribution to this controversy.

### Relevant Questions:

- Has feminizing or masculinizing hormone therapy in adolescents and adults been shown to be effective in improving patient-important outcomes such as relief of symptoms of GD, psychological well-being, sex-specific function, quality of life (QOL), functional status, or employment status?
- How does hormone therapy alone as a treatment for GD compare with sex reassignment surgery (SRS)?
- Is feminizing or masculinizing hormone therapy safe?
- Have definitive patient selection criteria been established for feminizing or masculinizing hormone therapy as a treatment for GD?

**Evidence Base:** Ten peer-reviewed studies, primarily of a cross-sectional or pretest-posttest design, assessing the effectiveness of hormone therapy plus 11 other studies with safety data for  $\geq 100$  adult patients or any safety data for adolescent patients.

**Search Dates:** Inception of databases to April 2014.

**Sample Sizes:** 50 to 376 pts (effectiveness); 1 to 2307 (safety).

**Patients:** Adult or adolescent patients with a diagnosis of GD. Mean age in effectiveness studies of adults, 29 to 45 years. Mean age in safety studies of adults, 41 to 52 years. Typical patients had not undergone either chest or genital SRS.

**Interventions:** Cross-sex hormone therapy or pubertal suppression therapy.

**Comparisons:** No medical treatment, SRS (chest and/or genital).

**Outcome Measures:** QOL, functional status, or employment status; psychological well-being (e.g., depression, self-esteem, reduced incidence of suicide); sexual function and satisfaction; and complications of hormone therapy, regret, or any other adverse event attributable to treatment.

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## Hormone-GD

**Follow-Up:** 3 months to 1 year (effectiveness studies, usually not reported); 2 to 23 years (safety studies).

**Findings:** Studies that evaluated hormone therapy in adults suggested the possibility of a small effect on QOL and function, specific psychological symptoms, social support, and alcoholism. The findings were inconsistent with respect to a relationship between hormone therapy and general psychological health, substance abuse, suicide attempts, and sexual function and satisfaction (9 studies).

**QOL/Functional Status (Adults):** 5 studies ( $\geq 812$  participants;  $\geq 796$  FtM) reported positive findings on  $\geq 1$  scale, but usually not on all scales used in the study. Differences between treated and untreated study participants were very small or of unknown magnitude in cross-sectional analyses that adjusted for potential confounders but were substantial in 1 pretest-posttest study.

**Psychological Symptoms (Adults):** In 6 studies, the results for a variety of specific psychological states (e.g., depression, anxiety) were positive, but overall measures of change in psychological symptomatology were mixed. In the studies that provided information on the magnitude of scales and/or cutoff points for normal ranges, the differences, if observed, were generally very small and scores for patients representing the control condition were typically already in the normal or mild range.

**Other Outcomes (Adults):** Improved social support and reduced alcoholism were suggested but the results regarding substance abuse were conflicting (2 studies). The prevalence of suicide attempts was not affected by hormone therapy (2 studies). Findings regarding the association of hormone therapy with sexual function and satisfaction were mixed (3 studies).

**Comparative Effectiveness of Hormone Therapy Alone Versus Surgery (Adults):** The evidence was too sparse to allow any conclusion regarding the comparative benefits of SRS and hormone therapy alone.

**Adolescents (Pubertal Suppression):** Evidence from a single small study was insufficient to suggest conclusions regarding the value of pubertal suppression therapy.

**Safety (Adults):** Hormone therapy has the potential to alter patients' risk of cardiovascular disease, cerebrovascular and thromboembolic events, osteoporosis, and cancer. The risk of no benefit must also be considered. There was an increased risk of cerebrovascular and thromboembolic events in MtF patients. There was *no* elevated risk of cancer in FtM patients. Hormone therapy and subsequent SRS failed to bring overall mortality, suicide rates, or death from illicit drug use in MtF patients close to rates observed in the general male population. It is possible that mortality is nevertheless reduced by these treatments, but that cannot be determined from the available evidence. Mortality data for FtM patients is less clear than for MtF patients. For safety issues other than the specific findings described here, the evidence was insufficient to suggest conclusions. There was no evidence concerning the prevalence of regret after hormone therapy.

**Safety (Adolescents):** The chief risks cited for pubertal suppression therapy are related to the possibility the GD could worsen because of the delay in definitive treatment. No serious side effects during pubertal suppression were reported. Older adolescents may begin cross-sex hormone therapy, but only a single case report provided long-term data for individuals who began therapy as adolescents. The body of evidence

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## Hormone-GD

concerning the safety of pubertal suppression and cross-sex hormone therapy in adolescents was too sparse and the studies too limited to suggest conclusions.

**Patient Selection Criteria:** The evidence is insufficient to support patient selection criteria for hormone therapy to treat GD. Professional associations recommend that hormone therapy be restricted to patients who have been referred for such treatment by a health professional who is qualified to assess GD. In adults, medical conditions that can be exacerbated by endocrine treatment must be evaluated and addressed prior to initiation of treatment. Practice guidelines advise that pubertal suppression therapy should not be initiated until adolescents have at least reached Tanner stage 2.

### **Quality of Evidence:** Very low.

Most studies were considered to be of very poor quality due to the nature of the study designs, failure to control for confounders, possible recall bias and selection bias, lack of blinded outcomes assessment, and/or unknown or short follow-up intervals. Not all positive results were statistically significant. For other outcomes, the findings were conflicting. For QOL and function, almost all of the available data were collected from FtM individuals for whom a diagnosis of GD could not be verified. For outcomes other than QOL and function, the quantity of evidence was very small. In safety studies, the relatively young age of study participants at the time of outcomes assessment and the lack of adjustment for risk factors in comparisons of study participants with age-matched general populations seriously diminishes the reliability of the available adverse event rates. No studies analyzed safety outcomes according to whether patients had undergone SRS, which is significant since hormone doses are lowered after SRS. The safety evidence described for adults in the **EXECUTIVE SUMMARY** is considered to be of low quality, but all other adult safety evidence was considered to be of very low quality.

**Conclusions:** A substantial number of studies of cross-sex hormone therapy each show some positive findings suggesting improvement in well-being after cross-sex hormone therapy. However, there are several serious limitations to the evidence.

Statistically significant improvements have not been consistently demonstrated by multiple studies for most outcomes. Five studies representing primarily female-to-male (FtM) adults reported modestly positive findings on  $\geq 1$  of the multiple quality of life (QOL) or functional scales for individuals who had undergone cross-sex hormone therapy, but for most of these individuals, a diagnosis of gender dysphoria (GD) was not confirmed. Evidence regarding QOL and function in male-to-female (MtF) adults was very sparse. Evidence for less comprehensive measures of well-being in adult recipients of cross-sex hormone therapy was directly applicable to GD patients but was sparse and/or conflicting. The study designs do not permit conclusions of causality and studies generally had weaknesses associated with study execution as well. There are potentially long-term safety risks associated with hormone therapy but none have been proven or conclusively ruled out. The evidence for adolescent populations was too sparse to suggest any conclusions.

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### Hayes Rating:

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**Hayes**

Transforming Healthcare with Evidence

MCHUGH 00014

## Hormone-GD

- C - For hormone therapy to treat GD in adults for whom a qualified mental health professional has made a formal diagnosis of GD and a recommendation for hormone therapy and who do not have any medical contraindications to endocrine therapy.

This Rating reflects the reporting of some positive evidence but serious limitations in the evidence of both effectiveness and safety. Also of concern is the fact that the magnitude of suggested benefit was typically small, which diminishes confidence in a true treatment effect.

- D2 - For pubertal suppression therapy or cross-sex hormone therapy in adolescents.

This Rating is based on a paucity of data.

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## INSIGHTS:

- Since part of the reason for the psychopathology experienced by transgender persons has to do with the reactions or expected reactions of family and society, evolving social norms theoretically could diminish the perceived need to undergo physical changes in order to live in the desired gender role.
- The benefits of hormone therapy appear to be of very small magnitude in the studies published to date. The literature does not provide guidance for assessing the clinical relevance of improvements in this population. One factor that may prevent the observation of large improvements is that individuals with a better social support and a better baseline psychological profile are probably seen to be better candidates by the mental health professionals who make recommendations for treatment.
- As the population of recipients of hormone therapy ages, better data concerning long-term safety risks should become available.
- Most studies have been performed in Europe. The results may not be generalizable to the United States.
- The studies selected for this report reflect the diagnostic criteria of DSM-IV, rather than the somewhat expanded criteria published in 2013 in the DSM-5.

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MCHUGH 00015



May 9, 2014

**Ancillary Procedures and Services for the Treatment of Gender Dysphoria****PURPOSE OF TECHNOLOGY:**

Some persons with gender dysphoria (GD) may seek hormone therapy and /or sex reassignment surgery (SRS) to resolve their incongruity between biological sex and gender identity. Additional ancillary surgeries or services, such as facial modifications, vocal cord surgery, or voice training, may be desired by transgender persons to further feminize or masculinize the body and/or perception of gender. In some cases, ancillary procedures are performed without SRS.

**EXECUTIVE SUMMARY:**

**Health Problem:** Individuals with gender dysphoria (GD) feel a severe incongruity between their biological sex and their gender identity. The prevalence of GD is 1 in 11,900 to 1 in 45,000 persons for male-to-female (MtF) and 1 in 30,400 to 1 in 200,000 persons for female-to-male (FtM) transgender persons.

The earlier term, *gender identity disorder* (GID), has given way to *gender dysphoria* (GD). This change was intended to reflect a consensus that gender nonconformity is not a psychiatric disorder, as it had been previously categorized. However, since the condition may cause clinically significant distress and since a diagnosis is necessary for access to medical treatment, the new term was proposed. The diagnostic criteria for GD outlined in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), Fifth Edition (DSM-V), as well as the criteria for GID in the DSM, Fourth Edition (DSM-IV), require that the individual believes there is a marked difference between the gender assigned to him or her by others and the gender he or she experiences or wishes to express. Additional criteria must also be met for a diagnosis of GD.

**Determinants:** The determinants of GD are poorly understood. Experts believe that gender identity develops as the result of a combination of biological factors, possibly including genetic and/or prenatal and perinatal hormonal influences, and environmental influences that have psychological effects.

**Treatment:** The treatment of GD is multifaceted. Psychotherapy helps the individual explore roles and expression and adopt various coping mechanisms to deal with societal and internal conflicts. Some transgender persons may seek hormone therapy to change their secondary sex characteristics and/or apply for sex reassignment surgery (SRS), which may include mastectomy/chest reconstruction or genital reconstruction. Additional ancillary surgeries or services, such as facial modifications, vocal cord surgery, or voice training, may be desired by transgender persons to further feminize or masculinize the body and/or perception of gender.

**Technology:** Ancillary procedures and services other than cross-sex hormone therapy or SRS for GD.

Some transgender persons desire procedures to feminize or masculinize their body and/or face. Also, some MtF transgender persons may desire voice therapy or vocal cord surgery to feminize their voice. Ancillary procedures include facial modifications, voice modification, reduction of the Adam's apple, enhancement of the buttocks, and permanent hair removal.

**Rationale:** Additional procedures may enhance the benefits of hormone therapy or SRS for GD, and for some individuals with GD, less comprehensive treatments may be sufficient for assuming the desired gender identity.

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**Short (Abbreviated) Title**

A transgender person who is readily accepted as their chosen gender may have a better quality of life and a reduction in the symptoms of GD.

**Controversy:** The medical necessity of treatments for GD is under debate. However, the condition does not readily fit traditional concepts of medical necessity since research to date has not established anatomical or physiological anomalies associated with GD. An evidence-based assessment of the effectiveness of ancillary procedures for alleviation of symptoms associated with GD and improvement of recipients' well-being can be a helpful contribution to this issue.

**Relevant Questions:**

- Have ancillary procedures and services been shown to be effective in improving patient-important outcomes such as relief of symptoms of GD or quality of life?
- Are ancillary procedures and services safe?
- Have definitive patient selection criteria been established for ancillary procedures and services as treatments for GD?

**Evidence Base:** Thirteen case series studies and chart reviews.

**Search Dates:** Inception of database to April 2014.

**Sample Sizes:** 10 to 76 patients; 1 study had 247 patients.

**Patients:** MtF (n=533) or FtM (n=3) adult transgender patients. It was not specified whether or not patients had a formal diagnosis of GD. The status of cross-sex hormone therapy or SRS among the study population was not reported by 4 of the studies. The remaining studies had variability regarding other GD treatments; however, none had inclusion criteria that specified these characteristics.

**Interventions:** Vocal cord surgery (5 studies), voice training (3 studies), rhinoplasty (2 studies), facial feminization surgery (2 studies), hair removal (1 study).

**Comparisons:** Twelve of the studies had no comparison group. One study of facial feminization surgery compared surgery recipients with patients who had not had facial surgery.

**Outcome Measures:** Patient satisfaction; voice characteristics; Voice Handicap Index; SF-36 Health Survey (QualityMetric Inc.) (1 study); grade, roughness, breathiness, asthenia, strain (GRBAS) Hirano scale.

**Follow-Up:** Mean of 6 to 30 months (5 studies did not report follow-up).

**Findings:** Patients were satisfied with the results of facial feminization and rhinoplasty; however, the results of vocal cord procedures and voice training were mixed.

**Vocal Cord Procedures:** Of the 5 reviewed studies of vocal cord surgery, 2 evaluated cricothyroid approximation, 2 evaluated laser vaporization, and 1 evaluated laryngoplasty. Cricothyroid approximation significantly raised the fundamental frequency of MtF transgender patients by a mean of 74 hertz (Hz). Laser vaporization significantly raised the fundamental frequency of MtF transgender patients by a mean of 48 Hz.

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**Short (Abbreviated) Title**

Feminization laryngoplasty significantly increased the fundamental frequency by 57 Hz. Patient satisfaction with the vocal cord surgery was variable, but the results suggest that patients were more satisfied following cricothyroid approximation than laser vaporization.

**Voice Training:** Three studies evaluated voice training as a method to increase the fundamental frequency of MtF transgender patients. The fundamental frequency increased by 14 to 28 Hz after voice training sessions and approximately half of the patients were satisfied with the outcome. One study evaluated voice training to decrease the fundamental frequency of 3 FtM patients; however, results of only 1 patient were available and his fundamental frequency decreased by 35 Hz after vocal training.

**Rhinoplasty:** Two studies evaluated feminization rhinoplasty on MtF transgender patients. All but 1 of the patients felt that their face had become more feminine in appearance and were satisfied with the results.

**Facial Feminization Surgery:** Two studies of facial feminization surgery were reviewed. In a retrospective case series study, MtF transgender patients who had various facial modification procedures felt that their faces had become more feminine in appearance. In a large retrospective cross-sectional study, quality of life was measured in MtF transgender patients who did or did not have facial feminization surgery. Patients who had facial feminization surgery were significantly more satisfied with their appearance than those who did not have facial surgery.

**Permanent Hair Removal:** One study of intense pulsed light epilation for permanent hair removal on MtF transgender patients was reviewed. After a mean of 9 epilation sessions, 90% of the patients achieved treatment success.

**Safety:** Most of the studies did not report complications; however, complications that were reported included bone nonunion following facial surgery (2% of patients); and dysphagia (34% of patients) or throat pain (29% of patients) following cricothyroid approximation.

**Patient Selection Criteria:** There is insufficient evidence to establish definitive patient selection criteria for ancillary procedures and services for the treatment of GD.

**Quality of Evidence:** Very low.

The individual study quality was generally very poor. The quality of the evidence was low because of study limitations, including small sample size and few studies evaluating each procedure category, lack of a control or comparator group, variable follow-up duration, inconsistent availability of results for all outcome measures, lack of baseline data for self-rated outcome measures, and lack of statistical analysis of results. Outcome measures were focused on technical success and patient satisfaction; only 1 study evaluated an overall measure of well-being using a validated instrument.

**Conclusions:** There is some evidence that transgender patients are satisfied with the results of rhinoplasty and facial feminization surgery, but patient satisfaction with vocal cord surgery and voice training was mixed. The evidence has serious limitations, and the effect of these procedures on overall individual well-being is unknown.

- Patients who had rhinoplasty or facial feminization surgery were generally pleased with the results.

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**Short (Abbreviated) Title**

- Vocal cord procedures and voice training had variable outcomes. Although the fundamental frequency was reduced by all treatment methods, patient satisfaction with the outcome was mixed.
- Most of the studies did not report complications; however, there was a low rate of bone nonunion following facial surgery, and moderate rates of dysphagia or throat pain following cricothyroid approximation.

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**Hayes Rating:**

**D2 - For vocal cord surgery for voice feminization in patients with GD.**

This Rating reflects the positive but limited evidence of this technology for transgender patients.

**D2 - For voice training for voice feminization in patients with GD.**

This Rating reflects the limited evidence of this technology for transgender patients, and conflicting results.

**D2 - For feminization rhinoplasty for patients with GD.**

This Rating reflects the limited evidence of this technology for transgender patients, and conflicting results.

**D2 - For facial feminization surgery in patients with GD.**

This Rating reflects the positive but limited evidence of this technology for transgender patients.

**D2 - For permanent hair removal technologies for patients with GD.**

This Rating reflects the positive but limited evidence of this technology for transgender patients.

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**INSIGHTS:**

- Since part of the reason for the psychopathology experienced by transgender persons has to do with the reactions or expected reactions of family and society, evolving social norms theoretically could diminish the perceived need to undergo physical changes in order to live in the desired gender role.
- As the population of recipients of ancillary procedures ages, better understanding concerning long-term safety risks should become available.

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# Growing Pains

## Problems with Puberty Suppression in Treating Gender Dysphoria

*Paul W. Hruz, Lawrence S. Mayer, and Paul R. McHugh*

Public controversies about how institutions should treat individuals who identify as a gender that does not correspond to their biological sex have recently been debated in the halls of government, in courtrooms, and on TV talk shows. Should males who identify as women have access to women's restrooms? Which school locker room should girls who identify as boys be permitted, or required, to use? Should teachers be compelled to use a student's preferred pronoun, or even a gender-neutral pronoun such as "ze" instead of "he" or "she"?

Alongside these questions of public concern, however, there are quieter matters of medicine and wellbeing. How should medical and mental health professionals care for patients who identify as the opposite sex, and how should families support loved ones who do so? The stakes are high: as detailed in a recent report in these pages, people who identify as transgender are disproportionately likely to suffer from a variety of mental health problems, including depression, anxiety, suicide attempts, and suicide.<sup>1</sup>

Psychiatrists who follow the American Psychiatric Association's *Diagnostic and Statistical Manual* use the term "gender dysphoria" for a condition in which "incongruence between one's experienced/expressed gender and assigned gender" is accompanied by "clinically significant distress or impairment in social, occupational, or other important areas of functioning."<sup>2</sup> In this context, "experienced/expressed gender" refers to

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the gender that the person subjectively identifies as or wishes to be publicly recognized as—what is often referred to as “gender identity”—while “assigned gender” refers in almost all cases to his or her unambiguous biological sex. (In rare cases, a person’s biological sex is difficult to determine; such “intersex” individuals are born with biological features of both sexes. Most transgender individuals are not biologically intersex.<sup>3</sup>)

There is strikingly little scientific understanding of important questions underlying the debates over gender identity—for instance, there is very little scientific evidence explaining why some people identify as the opposite sex, or why childhood expressions of cross-gender identification persist for some individuals and not for others.<sup>4</sup> Yet notwithstanding the limited data, physicians and mental health care providers have arrived at a number of methods for treating children, adolescents, and adults with gender dysphoria.

Of particular concern is the management of gender dysphoria in children. Young people with gender dysphoria constitute a singularly vulnerable population, one that experiences high rates of depression, self-harm, and even suicide.<sup>5</sup> Moreover, children are not fully capable of understanding *what it means* to be a man or a woman. Most children with gender identity problems eventually come to accept the gender associated with their sex and stop identifying as the opposite sex.<sup>6</sup> There is some evidence, however, that gender dysphoria and cross-gender identification become more persistent if they last into adolescence.<sup>7</sup>

In one prominent treatment approach, called “gender-affirming,” the therapist accepts, rather than challenges, the patient’s self-understanding as being the opposite sex. Gender-affirming models of treatment are sometimes applied even to very young children.<sup>8</sup> Often, the gender-affirming approach is followed in later youth and adulthood by hormonal and surgical interventions intended to make patients’ appearances align more closely with their gender identity than their biological sex. In order to improve the success of the physical changes, interventions at younger ages are increasingly being recommended.<sup>9</sup>

Gender identity clinics offering gender-affirmative psychotherapy for children and adolescents have opened for business in the United States and several other countries.<sup>10</sup> Though there is little systematically collected data on the number of young people (or even the number of adults) who identify as transgender or who have undergone sex-reassignment surgery,\* there is some evidence that the number of people receiving medical and psychotherapeutic care for gender identity issues is on the rise:

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- The Gender Identity Development Service in the United Kingdom, which treats only children under the age of 18, reports that it received 94 referrals of children in 2009/2010 and 1,986 referrals of children in 2016/2017—a relative increase of 2,000%.<sup>11</sup> The service also reports that it received six referrals for children under the age of 6 in 2009/2010, compared to thirty-two referrals for children under the age of 6 in 2016/2017—a relative increase of 430%.<sup>12</sup>
- In a brief paper by psychologists from a gender clinic in Toronto, the authors reported a large increase in the number of referrals for children (ages 3 to 12) per year between 1988 and 1991, when the number of children referred went from around 40 per year to around 80, a rate that remained steady through 2011.<sup>13</sup> The authors also reported that between 2004 and 2007, the rate of adolescents (ages 13 to 20) referred to their clinic rose from roughly 20 per year to 60, and then to nearly 100 per year by 2011.<sup>14</sup>
- In a paper by clinicians at Children’s Hospital Boston, the authors reported on the number of individuals who presented at the hospital with gender identity issues. Between 1998 and 2006, such patients presented to the hospital’s Endocrine Division at an average rate of 4.5 patients per year, but in the period from 2007 to 2009, after the hospital opened a gender identity clinic, the annual average of patients presenting with gender identity issues rose to 19 patients per year.<sup>15</sup>
- In a paper published in 2016, physicians from an Indianapolis pediatric endocrinology clinic reported a “dramatic increase” in referrals for gender dysphoria since 2002, finding that of 38 patients referred between 2002 and 2015, “74% were referred during the last 3 years.”<sup>16</sup> The authors emphasized that their clinic does not specialize in gender dysphoria, and that “the remarkable increase in the number of new patients seen in our clinic over the last 3 years has occurred even though our referral base is unchanged, and our clinic has not specifically advertised its care for transgender patients.”<sup>17</sup>

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\* The most familiar colloquial term used to describe the medical interventions that transform the appearance of transgender individuals may be “sex change” (or, in the case of surgery, “sex-change operation”), but this is not commonly used in the scientific and medical literature today. While no simple terms for these procedures are completely satisfactory—in the context of this article the most accurate description would be “hormonal and surgical interventions to modify secondary sex characteristics”—we employ the commonly used terms *sex reassignment* and *sex-reassignment surgery* or *procedures*, except when quoting a source that uses “gender reassignment” or some other term.

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The reasons for these rising rates are unclear. It may be that increased public awareness of gender dysphoria has made parents more willing to seek medical help for their children. (We should remember that it is parents or guardians, not children themselves, who make decisions about medical care.) However, the medical treatments provided for children with apparent symptoms of gender dysphoria, including affirmation of gender expression from the earliest evidence of cross-gender behaviors, may drive some children to persist in identifying as transgender when they might otherwise have, as they grow older, found their gender to be aligned with their sex. Gender identity for children is elastic (that is, it can change over time) and plastic (that is, it can be shaped by forces like parental approval and social conditions).<sup>18</sup> If the increasing use of gender-affirming care does cause children to persist with their identification as the opposite sex, then many children who would otherwise not need ongoing medical treatment would be exposed to hormonal and surgical interventions.

One particular gender-affirming intervention for children and young adolescents with gender dysphoria is puberty suppression (also known as puberty blocking)—a hormone intervention that prevents the normal progression of puberty. Puberty is a turbulent time in any young person's life, and it can be terrifying for those who identify as the opposite sex. For parents of children with gender dysphoria, puberty suppression can appear very attractive. It seems like it might offer a medical solution for the anticipated confusion, anxiety, and distress by holding back the development of the most conspicuous features of their children's biological sex. Puberty suppression seems to offer an intermediate step between the social affirmation that parents can give very young children and the sex-reassignment procedures that their kids can pursue once they've grown. And it seems to offer a way to mitigate the discordance between children's beliefs about their gender and the realities of their bodily development (while acquiescing to, rather than challenging, the children's self-understanding). Puberty suppression can, in short, look like safe passage from stormy seas of childhood expressions of beliefs about gender to the secure harbor of an adulthood lived permanently as the opposite sex.

In light of the growing prominence of gender identity issues in our society, and the appeal that puberty suppression may have for parents raising children who identify as the opposite sex, it is worth examining in detail what puberty suppression is, how it works, and whether it is as safe and prudent as its advocates maintain. As we shall see, the evidence for the safety and efficacy of puberty suppression is thin, based more on the subjective judgments of clinicians than on rigorous empirical evidence. It is,

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in this sense, still experimental—yet it is an experiment being conducted in an uncontrolled and unsystematic manner.

### What Is Puberty?

Having experienced adolescence and the tumultuous changes it involves, most adults are familiar in a very personal way with puberty. But addressing the questions surrounding puberty-blocking interventions for gender dysphoria requires acquaintance with how puberty is defined and understood in biology and medicine. Some fundamental facts about puberty are still unknown; in the words of one medical textbook, “Initiation of the onset of puberty has long been a mystery.”<sup>19</sup> But on the whole, the main aspects of puberty are well understood.

A textbook chapter by William A. Marshall and James M. Tanner (for whom the Tanner scale, a detailed measure of the stages of pubertal development is named) describes puberty as “the morphological and physiological changes that occur in the growing boy or girl as the gonads change from the infantile to the adult state. These changes involve nearly all the organs and structures of the body but they do not begin at the same age nor take the same length of time to reach completion in all individuals. Puberty is not complete until the individual has the physical capacity to conceive and successfully rear children.”<sup>20</sup> The authors go on to list the principal manifestations of puberty:

1. The adolescent growth spurt; i.e., an acceleration followed by a deceleration of growth in most skeletal dimensions and in many internal organs.
2. The development of the gonads.
3. The development of the secondary reproductive organs and the secondary sex characters.
4. Changes in body composition, i.e., in the quantity and distribution of fat in association with growth of the skeleton and musculature.
5. Development of the circulatory and respiratory systems leading, particularly in boys, to an increase in strength and endurance.<sup>21</sup>

The ability to physically conceive children is made possible by the maturation of the primary sex characteristics, the organs and structures that are involved directly in reproduction. In boys, these organs and structures include the scrotum, testes, and penis while in girls they include the

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ovaries, uterus, and vagina. In addition to these primary sex characteristics, secondary sex characteristics also develop during puberty—the distinctive physical features of the two sexes that are not directly involved in reproduction. Secondary sex characteristics that develop in girls include “the growth of breasts and the widening of the pelvis” and in boys “the appearance of facial hair and the broadening of shoulders,” while other patterns of body hair and changes in voice and skin occur during puberty in both girls and boys.<sup>22</sup>

Physicians characterize the progress of puberty by marking the onset of different developmental milestones. The earliest visible event, the initial growth of pubic hair, is known as “pubarche”; it occurs between roughly ages 8 and 13 in girls, and between ages 9.5 and 13.5 in boys.<sup>23</sup> In girls, the onset of breast development, known as “thelarche,” occurs around the same time as pubarche.<sup>24</sup> (The “-arche” in the terms for these milestones comes from the Greek for beginning or origin.) “Menarche” is another manifestation of sexual maturation in females, referring to the onset of menstruation, which typically occurs at around 13 years of age and is generally a sign of the ability to conceive.<sup>25</sup> Roughly corresponding to menarche in girls is “spermarche” in boys; this refers to the initial presence of viable sperm in semen, which also typically occurs around 13.<sup>26</sup>

### Hormones and Puberty

Having established *what* puberty is, we now turn to *how* puberty happens.

Scientists distinguish three main biological processes involved in puberty: adrenal maturation, gonadal maturation, and somatic growth acceleration.<sup>27</sup> We will discuss each of these processes in turn, with a particular focus on gonadal maturation.

“Adrenarche”—the beginning of adrenal maturation—begins between ages 6 and 9 in girls, and ages 7 and 10 in boys. The hormones produced by the adrenal glands during adrenarche are relatively weak forms of androgens (masculinizing hormones) known as dehydroepiandrosterone and dehydroepiandrosterone sulfate. These hormones are responsible for signs of puberty shared by both sexes: oily skin, acne, body odor, and the growth of axillary (underarm) and pubic hair.<sup>28</sup>

“Gonadarche”—the beginning of the process of gonadal maturation—normally occurs in girls between ages 8 and 13 and in boys between ages 9 and 14.<sup>29</sup> The process begins in the brain, where specialized neurons in the hypothalamus secrete gonadotropin-releasing hormone (GnRH).<sup>30</sup>

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This hormone is secreted in a cyclical or “pulsatile” manner<sup>31</sup>—the hypothalamus releases bursts of GnRH, and when the pituitary gland is exposed to these bursts, it responds by secreting two other hormones. These are luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which stimulate the growth of the gonads (ovaries in women and testes in men).<sup>32</sup> (The “follicles” that the latter hormone stimulates are not hair follicles but ovarian follicles, the structures in the ovaries that contain immature egg cells.) In addition to regulating the maturation of the gonads and the production of sex hormones, these two hormones also play an important role in regulating aspects of human fertility<sup>33</sup>—but for present purposes, we will focus on their role in the development of the gonads and the production of sex hormones during puberty.

As the gonadal cells mature under the influence of LH and FSH, they begin to secrete androgens (masculinizing sex hormones like testosterone) and estrogens (feminizing sex hormones).<sup>34</sup> These hormones contribute to the further development of the primary sex characteristics (the uterus in girls and the penis and scrotum in boys) and to the development of secondary sex characteristics (including breasts and wider hips in girls, and wider shoulders, breaking voices, and increased muscle mass in boys). The ovaries and testes both secrete androgens as well as estrogens, however the testes secrete more androgens and the ovaries more estrogens.<sup>35</sup>

The gonads and the adrenal glands are involved in two separate but interrelated pathways (or “axes”) of hormone signaling. These are the hypothalamic-pituitary-gonadal (HPG) axis and the hypothalamic-pituitary-adrenal (HPA) axis.<sup>36</sup> Though both play essential roles in puberty, it is, as just noted, the HPG axis that results in the development of the basic reproductive capacity and the external sex characteristics that distinguish the sexes.<sup>37</sup>

The third significant process that occurs with puberty, the somatic growth spurt, is mediated by increased production and secretion of human growth hormone, which is influenced by sex hormones secreted by the gonads (both testosterone and estrogen). Similar to the way that the secretion of GnRH by the hypothalamus provokes the pituitary gland to secrete FSH and LH, in this case short pulses of a hormone released by the hypothalamus cause the pituitary gland to release human growth hormone.<sup>38</sup> This process is augmented by testosterone and estrogen.<sup>39</sup> Growth hormone acts directly to stimulate growth in certain tissues, and also stimulates the liver to produce a substance called “insulin-like growth factor 1,” which has growth-stimulating effects on muscle.<sup>40</sup>

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The neurological and psychological changes occurring in puberty are less well understood than are the physiological changes. Men and women have distinct neurological features that may account for some of the psychological differences between the sexes, though the extent to which neurological differences account for psychological differences, and the extent to which neurological differences are caused by biological factors like hormones and genes (as opposed to environmental factors like social conditioning), are all matters of debate.<sup>41</sup>

Scientists distinguish between two types of effects hormones can have on the brain: organizational effects and activational effects. Organizational effects are the ways in which hormones cause highly stable changes in the basic architecture of different brain regions. Activational effects are the more immediate and temporary effects of hormones on the brain's activity. During puberty, androgens and estrogens primarily have activating effects, but long before then they have organizational effects in the brains of developing infants and fetuses.<sup>42</sup> (Some researchers speculate that cross-gender identification may be caused by atypical patterns of fetal exposure to sex hormones, but these theories have yet to be scientifically confirmed or even seriously tested.<sup>43</sup>) However, animal studies have provided some evidence that sex hormones may contribute to organizational effects (or reorganization) of the brain during puberty.<sup>44</sup> How, whether, and to what extent this process occurs in humans remain poorly understood.<sup>45</sup>

In sum: Puberty involves a myriad of complex, related, and overlapping physical processes, occurring at various points and lasting for various durations. Adrenarche and the secretion of growth hormones contribute to the child's growth and development, while gonadarche crucially leads to the maturation of sex organs that allow for reproduction, as well as the development of the other biological characteristics that distinguish males and females. The description offered here has been very simplified, of course, but it gives sufficient background to understand the workings of puberty suppression, to which we turn next.

### **The Origins of Puberty-Suppression Techniques**

Hormone interventions to suppress puberty were not developed for the purpose of treating children with gender dysphoria—rather, they were first used as a way to normalize puberty for children who undergo puberty too early, a condition known as “precocious puberty.”

For females, precocious puberty is defined by the onset of puberty before age 8, while for males it is defined as the onset of puberty before

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age 9.<sup>46</sup> Premature thelarche (the appearance of breast development) is usually the first clinical sign of precocious puberty in girls. For males, precocious puberty is marked by premature growth in genitalia and pubic hair.<sup>47</sup> In addition to the psychological and social consequences that a child might be expected to suffer, precocious puberty can also lead to reduced adult height, since the early onset of puberty interferes with later bone growth.<sup>48</sup>

Precocious puberty is divided into two types, central precocious puberty (sometimes labeled “true precocious puberty”) and peripheral precocious puberty (sometimes labeled “precocious pseudopuberty”).<sup>49</sup> Central precocious puberty is caused by the early activation of the gonadal hormone pathway by GnRH, and is amenable to treatment by physicians. Peripheral precocious puberty, which is caused by secretion of sex hormones by the gonads or adrenal glands independent of signals from the pituitary gland, is less amenable to treatment.<sup>50</sup> Precocious puberty is rare, especially in boys. A recent Spanish study of central precocious puberty estimated the overall prevalence to be 19 in 100,000 (37 in 100,000 girls affected, and 0.46 in 100,000 boys).<sup>51</sup> A Danish study of precocious puberty (not limited to central precocious puberty) found the prevalence to be between 20 to 23 per 10,000 in girls and less than 5 in 10,000 in boys.<sup>52</sup>

Treatment for precocious puberty is somewhat counterintuitive. Rather than stopping the production of GnRH, physicians actually provide patients more constant levels of synthetic GnRH (called GnRH analogues or GnRH agonists).<sup>53</sup> The additional GnRH “desensitizes” the pituitary, leading to a decrease in the secretion of gonadotropins (LH and FSH), which in turn leads to the decreased maturation of and secretion of sex hormones by the gonads (ovaries and testes). The first publication describing the use of GnRH analogues in children for precocious puberty appeared in 1981.<sup>54</sup>

The process of desensitization of the pituitary gland by synthetic GnRH is not permanent. After a patient stops taking the GnRH analogues, the pituitary will resume its normal response to the pulsatile secretion of GnRH by the hypothalamus, as evidenced by the fact that children treated for precocious puberty using GnRH analogues will resume normal pubertal development, usually about a year after they withdraw from treatment.<sup>55</sup>

In the time since GnRH analogues were first proposed in the early 1980s, they have become fairly well accepted as a treatment of precocious puberty, with one prominent GnRH analogue, Lupron, approved for that

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use by the FDA in 1993.<sup>56</sup> However, there remain some questions concerning the effectiveness of treatment with GnRH analogues. A recent consensus statement of pediatric endocrinologists concluded that GnRH analogues are an effective way to improve the height of girls with onset of puberty at less than 6 years of age, and also recommended the treatment be considered for boys with onset of precocious puberty who have compromised height potential.<sup>57</sup> Regarding the negative psychological and social outcomes associated with precocious puberty, the authors found that the available data were unconvincing, and that additional studies are needed.<sup>58</sup>

It is worth noting that the use of GnRH analogues has been considered in other contexts as well—for example, in some cases of children with severe learning disabilities, to ease the difficulties that those children and their caregivers may experience with puberty.<sup>59</sup> Synthetic GnRH to desensitize the pituitary has also been adapted to treat a variety of other conditions related to the secretion of sex hormones in adults, including prostate cancer<sup>60</sup> and fertility issues.<sup>61</sup> This is because the natural pulsatile release of GnRH continues to play an important role beyond puberty, in that it stimulates the pituitary gland to secrete gonadotropins that trigger the gonads to secrete sex hormones from the testes and ovaries.<sup>62</sup>

To sum up how puberty suppression works, a thought experiment might be helpful. Imagine two pairs of biologically and psychologically normal identical twins—a pair of boys and a pair of girls—where one child from each pair undergoes puberty suppression and the other twin does not. Doctors begin administering GnRH analogue treatments for the girl at, say, age 8, and for the boy at age 9. Stopping the gonadal hormone pathway of puberty does not stop time, so the puberty-suppressed twins will continue to age and grow—and because adrenal hormones associated with puberty will not be affected, the twins receiving GnRH analogue will even undergo some of the changes associated with puberty, such as the growth of pubic hair. However, there will be major, obvious differences within each set of twins. The suppressed twins' reproductive organs will not mature: the testicles and penis of the boy undergoing puberty suppression will not mature, and the girl undergoing puberty suppression will not menstruate. The boy undergoing puberty suppression will have less muscle mass and narrower shoulders than his twin, while the breasts of the girl undergoing puberty suppression will not develop. The boy and girl undergoing puberty suppression will not have the same adolescent growth spurts as their twins. So all told, by the time the untreated twins reach maturity, look like adults, and are biologically capable of having

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children, the twins undergoing puberty suppression will be several inches shorter, will physically look more androgynous and childlike, and will not be biologically capable of having children. This is only a thought experiment, but it illustrates some of the effects that puberty suppression would be expected to have on the development of a growing adolescent's body.

### Advocacy and Guidelines

A number of medical associations and advocacy groups have endorsed puberty suppression as a prudent and compassionate way of helping youth with gender dysphoria. In 2009, the Endocrine Society—an international organization of professionals who deal with the body's hormones—published guidelines for the treatment of transsexual persons, recommending “that adolescents who fulfill eligibility and readiness criteria for gender reassignment initially undergo treatment to suppress pubertal development.”<sup>63</sup>

Two years later, the Endocrine Society partnered with other organizations—the World Professional Association for Transgender Health, the European Society of Endocrinology, the European Society of Pediatric Endocrinology, and the Pediatric Endocrine Society—to circulate another set of guidelines for the treatment of transgender individuals.<sup>64</sup> Three observations are provided in the guidelines to justify puberty suppression. First, gender dysphoria “rarely desists after the onset of pubertal development” and additionally, “suppression causes no irreversible or harmful changes in physical development and puberty resumes readily if hormonal suppression is stopped.”<sup>65</sup> Second, the typical physical changes of puberty are “often associated with worsening of gender dysphoria,” which has “been reversed by pubertal suppression.”<sup>66</sup> Third, the modification of secondary sex characteristics by hormonal treatments “is easier and safer when the sex steroids of the adolescent's genetic sex and their physical effects, for example, virilization of breast growth, are not present.”<sup>67</sup>

The World Professional Association for Transgender Health (WPATH, a membership organization for health care professionals that advocates for transgender health care) also endorses puberty suppression in its *Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People* (2011), if the following criteria are met:

1. The adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria (whether suppressed or expressed);

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2. Gender dysphoria emerged or worsened with the onset of puberty;
3. Any coexisting psychological, medical, or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start treatment;
4. The adolescent has given informed consent and, particularly when the adolescent has not reached the age of medical consent, the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process.<sup>68</sup>

The *WPATH Standards of Care* document gives the following two justifications for puberty suppression interventions: “(i) their use gives adolescents more time to explore their gender nonconformity and other developmental issues; and (ii) their use may facilitate transition [to living as the opposite sex] by preventing the development of sex characteristics that are difficult or impossible to reverse if adolescents continue on to pursue sex reassignment.”<sup>69</sup>

In 2016, the Human Rights Campaign, an LGBT advocacy group, partnered with the American Academy of Pediatrics—the nation's most prominent professional organization for pediatricians—and the American College of Osteopathic Pediatricians to publish a guide for families of transgender children. The guide says that “to prevent the consequences of going through a puberty that doesn't match a transgender child's identity, healthcare providers may use fully reversible medications that put puberty on hold.”<sup>70</sup> Delaying puberty, according to the guide, gives the child and family time “to explore gender-related feelings and options.”<sup>71</sup>

Reading these various guidelines gives the impression that there is a well-established scientific consensus about the safety and efficacy of the use of puberty-blocking agents for children with gender dysphoria, and that parents of such children should think of it as a prudent and scientifically proven treatment option. But whether blocking puberty is the best way to treat gender dysphoria in children remains far from settled and it should be considered not a prudent option with demonstrated effectiveness but a drastic and experimental measure.

Experimental medical treatments for children must be subject to especially intense scrutiny, since children cannot provide legal consent to medical treatment of any kind (parents or guardians must consent for their child to receive treatment), to say nothing of consenting to become research

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subjects for testing an unproven therapy. In the case of gender dysphoria, however, the safety and efficacy of puberty-suppressing hormones is not well founded on evidence—though hormone interventions used for suppressing puberty in children have undergone clinical trials, these trials were, as discussed above, for other indications, such as delaying precocious puberty. Whether puberty suppression is safe and effective when used for gender dysphoria remains unclear and unsupported by rigorous scientific evidence. This is especially worrying in light of the lack of understanding of the causes of gender dysphoria in children or adults. Conditions like precocious puberty, for instance, have a biological course that is relatively well understood. Hormone interventions that treat that condition are tailored to its causes. In the case of gender dysphoria, however, we simply do not know what causes a child to identify as the opposite sex, so medical interventions, like puberty suppression, cannot directly address it.

Some doctors who use puberty suppression to treat children with gender dysphoria argue that “the etiology does not affect the way adolescents with GD [gender dysphoria] should be treated”<sup>72</sup>—that is, treating gender dysphoria does not require us first to understand its causes. In an analogy offered by one anonymous psychiatrist interviewed in a study of physicians’ attitudes on the subject, “even if you do not know exactly why or how [a] person has broken his leg,” it is possible to “understand that it is painful and impairs function.”<sup>73</sup> Though there are obvious differences between the importance of the etiology of incidental injuries (like a broken leg) and persistent psychological conditions (like gender dysphoria), this comparison is worth considering carefully. It is true that caring for patients is important regardless of the etiology of their conditions. However, even for an injury like a broken bone, a doctor should be interested in (for example) whether the patient has some condition that makes his or her bones more breakable. A bone fracture may be a symptom of an underlying pathology such as osteoporosis, and in such cases, different courses of treatment may be indicated; the bone may need to set for longer, and doctors will generally recommend certain lifestyle changes or extensive courses of treatment to mitigate the underlying condition and to reduce the risk of future injuries.

If we understood the underlying causes of gender dysphoria (or even factors that contribute to the risk and severity of gender dysphoria, as osteoporosis is a risk factor in bone fractures), doctors would be able to make different kinds of recommendations to patients for mitigating the underlying disconnection between the gender identity and the body of a patient, and reducing the severity of the dysphoria experienced by their

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patients. All discussions of appropriate treatments for gender dysphoria in adolescents or adults are subject to the qualification that entirely new therapeutic approaches might be discovered as a result of improvements in our currently limited understanding of the etiology and course of gender dysphoria.

Puberty suppression as an intervention for gender dysphoria has been accepted so rapidly by much of the medical community, apparently without scientific scrutiny, that there is reason to be concerned about the welfare of children who are receiving it, as well as reason to question the veracity of some of the claims made to support its use—such as the assertion that it is physiologically and psychologically “reversible.” To better understand the treatment options for children with gender dysphoria, it is worth examining the origins of this approach and the justifications offered for it.

### **Blocking Puberty for Gender Dysphoria**

During the 1980s, at about the same time that GnRH-based treatments for precocious puberty were being developed, another use of the technique was being tested: to suppress the normal physiological production of male sex hormones among adult males who identify as females. This form of hormonal sex reassignment was first described in 1981, when Canadian doctors reported their use of GnRH analogues to suppress androgen production in four transsexual males, ages 18 to 29.<sup>74</sup> GnRH analogues continue to be used as part of sex-reassignment procedures for some adult male-to-female sex reassignment patients.<sup>75</sup>

It was only in the 1990s that GnRH analogues came to be used for the first time to suppress puberty in children who identify as the opposite sex. In 1998, Peggy Cohen-Kettenis and Stephanie van Goozen, psychologists at a Dutch gender clinic, described the case of a 13-year-old female gender-dysphoria patient. GnRH analogue was used to suppress puberty before she received a definitive diagnosis of gender identity disorder at age 16. (Gender identity disorder was then the generally accepted term for what is now more often called gender dysphoria, although the two are not identical.) At age 18, she underwent sex-reassignment surgery.<sup>76</sup> The clinic’s scientists and physicians went on to develop an influential protocol for using puberty suppression as part of a gender-affirming therapeutic approach to gender dysphoria and gender identity issues in adolescents. A description of the protocol was published in the *European Journal of Endocrinology* in 2006,<sup>77</sup> with another paper describing “changing insights” into the use

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of puberty suppression in adolescents published in the *Journal of Sexual Medicine* in 2008.<sup>78</sup>

The protocol, often referred to as the “Dutch protocol,” calls for puberty suppression to begin at age 12 after a diagnosis of gender identity disorder. The protocol stipulates that the diagnosis should be made by both a psychologist and a psychiatrist, after information is “obtained from both the adolescent and the parents on various aspects of general and psychosexual development of the adolescent, the adolescent’s current functioning and functioning of the family.”<sup>79</sup> The researchers’ method for suppressing puberty was to inject 3.75 milligrams of the GnRH analogue triptorelin every four weeks.<sup>80</sup> With this regimen, “there was no progression of the pubertal stage,” and “regression of the first stages of the already developed sex characteristics.” This meant that, in girls, “breast tissue will become weak and may disappear completely,” and in boys, “testicular volume will regress to a lower volume.”<sup>81</sup>

Then, starting at age 16, cross-sex hormones are administered while GnRH analogue treatment continues, in order to induce something like the process of puberty that would normally occur for members of the opposite sex. In female-to-male patients, testosterone administration leads to the development of “a low voice, facial and body hair growth, and a more masculine body shape” as well as to clitoral enlargement and further atrophy of breast tissue.<sup>82</sup> In patients seeking a male-to-female transition, the administration of estrogens will result in “breast development and a female-appearing body shape.” Cross-sex hormone administration for these patients will be prescribed for the rest of their lives.<sup>83</sup>

Surgery is prescribed for patients once they reach 18 years of age, though “if the patient is not satisfied with, or is ambivalent about, the hormonal effects or surgery, the applicant is not referred for surgery.”<sup>84</sup> Male-to-female surgery involves the construction of “female-looking external genitals” (which involves the removal of the testes), in addition to breast enlargement if estrogen therapy has not resulted in satisfactory breast growth.<sup>85</sup> For female-to-male patients, the first surgery is often mastectomy; some female-to-male patients elect not to undergo the phalloplasty (the surgical construction of a penis), since the quality and functionality of such surgically constructed “neopenises” vary.<sup>86</sup> Removal of the uterus and ovaries are also common surgical procedures for female-to-male patients.<sup>87</sup> After the surgical removal of the gonads (testes in male-to-female patients or ovaries in female-to-male), the patients then discontinue GnRH analogue treatment, since the signaling pathway from GnRH to the pituitary gland will no longer result in the production

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of sex hormones once the gonads are removed.<sup>88</sup> Some of the surgical operations involved in sex reassignment, such as breast augmentation, are primarily cosmetic; others, such as the removal of gonads, have significant biological effects in that they impair or eliminate the individual's natural reproductive capacities and ability to produce important sex hormones. However, none of the surgeries or hormone treatments currently possible confer the reproductive capacities of the opposite sex.

According to researchers at the Dutch clinic, some of the known effects of puberty suppression on physiologically normal children are what you would expect from alterations made to that critical stage of human development. It has a significant negative effect on the height growth rates of both male-to-female and female-to-male patients.<sup>89</sup> The female-to-male patients subsequently experienced a growth spurt when androgens were administered, whereas for male-to-female patients, estrogen treatment "may result in a more appropriate 'female' final height."<sup>90</sup> The development of normal bone-mineral density is another concern for children and adolescents treated with puberty-suppressing hormones. Early reports suggested that the patients may have experienced reduced development of bone-mineral density while on puberty-suppressing treatments, though density increased when cross-sex hormone treatments began.<sup>91</sup> Other more recent reports are mixed; one paper found that, although bone mass did not decline during puberty suppression, the children undergoing puberty suppression fell behind the average rates of bone-density growth for their age,<sup>92</sup> while another reported that puberty suppression resulted in decreased bone growth in adolescents with gender dysphoria.<sup>93</sup>

In the United States, the treatment of gender dysphoria is not yet an FDA-approved use for GnRH analogue drugs (although treatments for precocious puberty, prostate cancer, and other conditions are approved).<sup>94</sup> This means that puberty suppression relies on the "off-label" prescription of GnRH analogue treatments; doctors are permitted to use these drugs in treating children with gender dysphoria, but the lack of FDA approval means that pharmaceutical companies selling the drugs cannot market them for treating gender dysphoria. Off-label status reflects that the use has not been proven in clinical trials to be safe and effective.

### **Weak Justifications**

Modifying biologically normal development in 12-year-olds to treat a psychiatric condition is a serious step, one that the scientists who developed the Dutch protocol attempt to justify with a number of arguments.

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First, they argue that blocking puberty may mitigate the psychosocial difficulties experienced by adolescents with gender dysphoria by lessening the growing incongruity between the adolescent patient's gender identity and sex.<sup>95</sup> They also argue that mitigating the early development of secondary sex characteristics during puberty can make the eventual transition (both medical and social) to living as the opposite sex easier.<sup>96</sup>

For patients and doctors who are committed to the view that the young person's gender dysphoria represents a persistent and real problem that can best be solved by transitioning the patient to living as the opposite sex, puberty suppression can seem like a desirable approach. But most children who identify as the opposite sex will not persist in these feelings and will eventually come to identify as their biological sex: According to the *Diagnostic and Statistical Manual of Mental Disorders*, "In natal [biological] males, persistence [of gender dysphoria] has ranged from 2.2% to 30%. In natal females, persistence has ranged from 12% to 50%."<sup>97</sup> (As noted earlier, there is some evidence that cross-gender identification becomes more persistent if it lasts into adolescence.<sup>98</sup>) The relatively low levels of persistence pose a challenge for those who would use puberty-suppressing treatments for young children—and for those who recommend encouraging and affirming children in their cross-gender identification. The epidemiologically low persistence rates suggest that puberty suppression would not be wise for all children who experience gender dysphoria, since it would be an unnecessary treatment for those children whose gender dysphoria would not persist if they received no intervention, and it is generally considered best, in clinical practice, to avoid unnecessary medical interventions. And beyond *unnecessary*, the interventions could, in some cases, be *harmful*, if they lead children whose gender dysphoria may have resolved in adolescence to instead persist in a dysphoric condition.

In a 2008 article, the Dutch scientists respond to this concern—the possibility that young adolescents might undergo medical interventions that could ultimately be unnecessary or worse—by arguing that adolescents who continue to identify as the opposite sex and who continue to desire sex reassignment into early puberty rarely come to identify as their biological sex; they also note that none of their own patients who were found eligible for sex reassignment decided against it.<sup>99</sup> But the fact that none of the patients for whom they recommended sex reassignment decided against the procedure may either indicate that their recommendations were based on a sound diagnosis of persistent gender dysphoria, *or* that their diagnosis—along with the course of treatment that followed

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from it, including gender-affirmative psychotherapy and puberty suppression—may have solidified the feelings of cross-gender identification in these patients, leading them to commit more strongly to sex reassignment than they might have if they had received a different diagnosis or a different course of treatment.

The criteria used by the Dutch scientists to ensure that puberty-suppressing drugs are used only in appropriate cases do little to alleviate the concern that such treatments might make feelings of cross-gender identification more persistent:

- i) a presence of gender dysphoria from early childhood on; (ii) an increase of the gender dysphoria after the first pubertal changes; (iii) an absence of psychiatric comorbidity that interferes with the diagnostic work-up or treatment; (iv) adequate psychological and social support during treatment; and (v) a demonstration of knowledge and understanding of the effects of GnRH, cross-sex hormone treatment, surgery, and the social consequences of sex reassignment.<sup>100</sup>

It is worth closely examining some of these criteria. The first criterion, that gender dysphoria is present from early childhood on, seems to assume that a patient's identification as the other gender will endure if the patient has felt that way for a long time. But signs of gender dysphoria in children are even more vague and unreliable than signs of gender dysphoria in adolescents and adults; diagnoses of gender dysphoria in children rely more on gender-atypical behaviors (for example, boys playing with dolls or girls preferring to play with boys) than on a committed belief on the part of the patients that they "really are" the opposite sex. While an increasing severity of gender dysphoria around the onset of puberty (the second criterion) may be associated with the long-term persistence of gender dysphoria, it is difficult to separate this from the possibility that the "psychological and social support" for the child's cross-gender feelings, behaviors, and identification (the fourth criterion) may have contributed to the persistence of the child's gender dysphoria. And regarding the fifth and final criterion, it seems difficult to expect that a 12-year-old would have an understanding of the effects of these complex medical interventions and of the "social consequences of sex reassignment" when these are matters that are poorly understood by doctors and scientists themselves. Furthermore, whether children as young as 12 fully understand their gender identity and whether they can be diagnosed reliably as having persistent gender dysphoria are difficult psychological questions that cannot be separated from medical judgments about the appropriateness of puberty suppression.

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In the same 2008 paper, the authors write that providing pubertal suppression allows patients to avoid the “alienating experience of developing sex characteristics, which they do not regard as their own” and it “is also proof of solidarity of the health professional with the plight of the applicant.”<sup>101</sup> Though it is important for physicians to establish a relationship of trust and compassion with their patients, for physicians to offer “proof of solidarity” to patients by acceding to their wishes, regardless of whether the patients’ wishes are in their best medical interests, is far from the Hippocratic tradition and surrenders the physician’s responsibility to treat patients with their ultimate benefit in mind.

### Claims of “Reversibility”

A major selling point for puberty suppression is the claim that the procedure is “fully reversible.”<sup>102</sup> This assertion allows advocates to make puberty suppression seem like a prudent compromise between two extremes: not providing any medical treatment for young patients diagnosed with gender dysphoria, which would seem negligent, and immediately and permanently medically altering the sexual characteristics of children, which would seem reckless.

Some claims of reversibility:

- The Dutch scientists who developed the protocol for puberty suppression describe it as “fully reversible.”<sup>103</sup>
  - Pediatric endocrinologist Daniel Metzger says that “the effect of the puberty-blocking drugs is reversible.”<sup>104</sup>
  - Norman Spack, a physician at Boston’s Children Hospital who treats gender dysphoria, describes puberty-suppressing drugs as “totally reversible.”<sup>105</sup>
  - In a review of the research on puberty-blocking drugs for an LGBT advocacy group, Laura E. Kuper, a researcher focused on transgender health, describes puberty blocking as “fully reversible.”<sup>106</sup>
  - Transgender journalist Mitch Kellaway, writing for the website Advocate.com about how “blocking puberty is beneficial for transgender youth,” describes puberty blocking as “fully reversible.”<sup>107</sup>
  - In another Advocate.com story about puberty blocking, transgender activist Andrea James writes that “the treatment is reversible.”<sup>108</sup>
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- Bioethicist Arthur Caplan has described puberty blocking as reversible, saying that “if it’s decided to stop the treatment, puberty will resume.”<sup>109</sup>
- Pediatric endocrinologists Christopher P. Houk and Peter A. Lee write that puberty suppression in children with gender dysphoria is “reversible.”<sup>110</sup>

A twist on the theme of reversibility appears in the guide for supporting and caring for transgender children published in 2016 by the Human Rights Campaign. The document highlights how “extremely distressing” the development of secondary sex characteristics can be for transgender youth, and even notes that “some of these physical changes, such as breast development, are *irreversible* or require surgery to undo” (emphasis added).<sup>111</sup> Similar language is used by the scientists who developed the Dutch protocol, who write that “the child who will live permanently in the desired gender role as an adult may be spared the torment of (full) pubescent development of the ‘wrong’ secondary sex characteristics”<sup>112</sup> and elsewhere write that puberty suppression is important because the development of secondary sex characteristics that cause a transgender person to look “like a man (woman) when living as a woman (man)...is obviously an enormous and lifelong disadvantage.”<sup>113</sup> This turns the normal language of reversibility on its head, speaking of the natural process of biological development as an irreversible series of problems that medicine should seek to prevent, while presenting the intervention—puberty suppression—as benign and reversible.

One common argument based on the idea that puberty suppression is a reversible and prudent first step is that it can, as the Dutch scientists put it, “give adolescents, together with the attending health professional, more time to explore their gender identity, without the distress of the developing secondary sex characteristics. The precision of the diagnosis may thus be improved.”<sup>114</sup> There is much that is strange about this argument. It presumes that natural sex characteristics interfere with the “exploration” of gender identity, when one would expect that the development of natural sex characteristics might contribute to the natural consolidation of one’s gender identity. It also presumes that interfering with the development of natural sex characteristics can allow for a more accurate diagnosis of the gender identity of the child. But it seems equally plausible that the interference with normal pubertal development will influence the gender identity of the child by reducing

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the prospects for developing a gender identity corresponding to his or her biological sex.

Given its potential importance in the lives of the affected children, it is worth carefully examining these claims about reversibility. In developmental biology, it makes little sense to describe anything as “reversible.” If a child does not develop certain characteristics at age 12 because of a medical intervention, then his or her developing those characteristics at age 18 is not a “reversal,” since the sequence of development has already been disrupted. This is especially important since there is a complex relationship between physiological and psychosocial development during adolescence. Gender identity is shaped during puberty and adolescence as young people’s bodies become more sexually differentiated and mature. Given how little we understand about gender identity and how it is formed and consolidated, we should be cautious about interfering with the normal process of sexual maturation.

Rather than claiming that puberty suppression is reversible, researchers and clinicians should focus on the question of whether the physiological and psychosocial development that occurs during puberty can resume in something resembling a normal way after puberty-suppressing treatments are withdrawn. In children with precocious puberty, this does appear to be the case. Puberty-suppressing hormones are typically withdrawn around the average age for the normal onset of gonadarche, at about age 12, and normal hormone levels and pubertal development gradually resume. For one common method of treating precocious puberty, girls reached menarche approximately a year after their hormone treatments ended, at an average age of approximately 13, essentially the same average age as the general population.<sup>115</sup>

However, the evidence for the safety and efficacy of puberty suppression in boys is less robust, chiefly since precocious puberty is much more rare in boys. Although the risks are speculative and based on limited evidence, boys who undergo puberty suppression may be at greater risk for the development of testicular microcalcifications, which may be associated with an increased risk of testicular cancer, and puberty suppression in boys may also be associated with obesity.<sup>116</sup>

Most critically, unlike children affected by precocious puberty, adolescents with gender dysphoria do not have any physiological disorders of puberty that are being corrected by the puberty-suppressing drugs. The fact that children with suppressed precocious puberty between ages 8 and 12 resume puberty at age 13 does not mean that adolescents suffering from gender dysphoria whose puberty is suppressed beginning at

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age 12 will simply resume normal pubertal development down the road if they choose to withdraw from the puberty-suppressing treatment and choose not to undergo other sex-reassignment procedures. Another troubling question that has been largely uninvestigated is what psychological consequences there might be for children with gender dysphoria whose puberty has been suppressed and who later come to identify as their biological sex.

Though there is very little scientific evidence relating to the effects of puberty suppression on children with gender dysphoria—and there certainly have been no controlled clinical trials comparing the outcomes of puberty suppression to the outcomes of alternative therapeutic approaches—there are reasons to suspect that the treatments could have negative consequences for neurological development. Scientists at the University of Glasgow recently used puberty-suppressing treatments on sheep, and found that the spatial memory of male sheep was impaired by puberty suppression using GnRH analogues,<sup>117</sup> and that adult sheep that were treated with GnRH analogues near puberty continued to show signs of impaired spatial memory.<sup>118</sup> In a 2015 study of adolescents treated with puberty suppression, the authors claimed that “there are no detrimental effects of [GnRH analogues] on [executive functioning],”<sup>119</sup> but the results of their study were more ambiguous and more suggestive of harm than that summary indicates.<sup>120</sup> (It is also worth noting that the study was conducted on a small number of subjects, which makes the detection of significant differences difficult.)

In addition to the reasons to suspect that puberty suppression may have side effects on physiological and psychological development, the evidence that something like normal puberty will resume for these patients after puberty-suppressing drugs are removed is very weak. This is because there are virtually no published reports, even case studies, of adolescents withdrawing from puberty-suppressing drugs and then resuming the normal pubertal development typical for their sex. Rather than resuming biologically normal puberty, these adolescents generally go from suppressed puberty to medically conditioned cross-sex puberty, when they are administered cross-sex hormones at approximately age 16. During this time, as per the Dutch protocol, puberty-suppressing GnRH analogues continue to be administered to prevent the initiation of gonadarche; the sex hormones that are normally secreted by the maturing gonads are not produced, and physicians administer sex hormones normally produced by the gonads of the opposite sex. This means that adolescents undergoing cross-sex hormone treatment circumvent the most fundamental form of

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sexual maturation—the maturation of their reproductive organs. Patients undergoing sex reassignment discontinue GnRH treatment after having their gonads removed, since the secretion of sex hormones that the treatment is ultimately intended to prevent will no longer be possible.

Today’s medical technology does not make it possible for a patient to actually grow the sex organs of the opposite sex. Instead, doctors focus on preventing the maturation of primary sex characteristics and manipulating secondary sex characteristics through the administration of hormones. Infertility is therefore one of the major side effects of the course of treatment that runs from puberty suppression through cross-sex hormones to surgical sex reassignment.

After the surgical removal of ovaries or testes, which the Dutch protocol recommends for young adults with gender dysphoria at around age 18, the possibility of normal pubertal development becomes impossible, since it is these organs that normally produce the androgens and estrogens responsible for the development of secondary sex characteristics. Even though the secretion of GnRH by the hypothalamus may continue to stimulate the pituitary to secrete gonadotropins, if the gonads themselves are physically removed from the body, these hormonal signals become virtual “dead letters.”

Because the major studies of puberty suppression have not reported results of patients who have withdrawn from treatment and then resumed the puberty typical of their sex, we also do not know how normally the primary and secondary sex characteristics will develop in adolescents whose puberty has been artificially suppressed beginning at age 12. And so the claim that puberty suppression for adolescents with gender dysphoria is “reversible” is based on speculation, not rigorous analysis of scientific data.

The lack of data on gender dysphoria patients who have withdrawn from puberty-suppressing regimens and resumed normal development raises again the very important question of whether these treatments contribute to the persistence of gender dysphoria in patients who might otherwise have resolved their feelings of being the opposite sex. As noted above, most children who are diagnosed with gender dysphoria will eventually stop identifying as the opposite sex. The fact that cross-gender identification apparently persists for virtually *all* who undergo puberty suppression could indicate that these treatments increase the likelihood that the patients’ cross-gender identification will persist.

As philosopher Ian Hacking has argued, many psychological conditions are subject to what he calls a “looping effect,” wherein the classification of

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people as belonging to certain “kinds” can change how those people think of themselves and how they behave.<sup>121</sup> Children and adolescents who are experiencing confusion about gender roles, their sexuality and behavior, and the changes caused by puberty may be especially likely to take up the way of life provided for by a “kind” like “transgender” as a way to make sense of their confusing circumstances, especially when they are subjected to the pressure of being labeled as such by adults in positions of authority, including parents, teachers, psychologists, and physicians.

### **What We Don't Know Can Hurt Us**

The use of puberty suppression and cross-sex hormones for minors is a radical step that presumes a great deal of knowledge and competence on the part of the children assenting to these procedures, on the part of the parents or guardians being asked to give legal consent to them, and on the part of the scientists and physicians who are developing and administering them. We frequently hear from neuroscientists that the adolescent brain is too immature to make reliably rational decisions,<sup>122</sup> but we are supposed to expect emotionally troubled adolescents to make decisions about their gender identities and about serious medical treatments at the age of 12 or younger. And we are supposed to expect parents and physicians to evaluate the risks and benefits of puberty suppression, despite the state of ignorance in the scientific community about the nature of gender identity.

The claim that puberty-blocking treatments are fully reversible makes them appear less drastic, but this claim is not supported by scientific evidence. It remains unknown whether or not ordinary sex-typical puberty will resume following the suppression of puberty in patients with gender dysphoria. It is also unclear whether children would be able to develop normal reproductive functions if they were to withdraw from puberty suppression. It likewise remains unclear whether bone and muscle development will proceed normally for these children if they resume puberty as their biological sex. Furthermore, we do not fully understand the psychological consequences of using puberty suppression to treat young people with gender dysphoria.

More research is needed to resolve these unanswered questions. At the same time, research into how and why gender dysphoria occurs, persists, and desists must also continue, as it could elucidate new ways to help people cope with gender dysphoria with less permanent and drastic treatments than sex reassignment.

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In light of the many uncertainties and unknowns, it would be appropriate to describe the use of puberty-blocking treatments for gender dysphoria as experimental. And yet it is not being treated as such by the medical community. Over the course of decades, experimental medicine has developed many norms, standards, and protocols, including human subjects protections, the use of institutional review boards, and carefully controlled clinical trials, as well as long-term follow-up studies. These longstanding practices are meant to make experimental medicine more rigorous and to serve the interests of patients, physicians, and the community. But when it comes to the use of puberty-blocking treatments for gender dysphoria, these standards and protocols seem to be almost entirely absent—a fact that ill serves patients, physicians, the community, and the search for truth. Physicians should be cautious about embracing experimental therapies in general, but especially those intended for children, and should particularly avoid any experimental therapy that has virtually no scientific evidence of effectiveness or safety. Regardless of the good intentions of the physicians and parents, to expose young people to such treatments is to endanger them.

While there is much that is not known with certainty about gender dysphoria, there is clear evidence that patients who identify as the opposite sex often suffer a great deal. They have higher rates of anxiety, depression, and even suicide than the general population. Something must be done to help these patients, but as scientists struggle to better understand what gender dysphoria is and what causes it, it would not seem prudent to embrace hormonal treatments and sex reassignment as the foremost therapeutic tools for treating this condition.

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with gender dysphoria who had not undergone puberty suppression, or from females with gender dysphoria who had undergone puberty suppression.

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# Long-Term Follow-Up of Transsexual Persons Undergoing Sex Reassignment Surgery: Cohort Study in Sweden

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## Abstract

**Context:** The treatment for transsexualism is sex reassignment, including hormonal treatment and surgery aimed at making the person's body as congruent with the opposite sex as possible. There is a dearth of long term, follow-up studies after sex reassignment.

**Objective:** To estimate mortality, morbidity, and criminal rate after surgical sex reassignment of transsexual persons.

**Design:** A population-based matched cohort study.

**Setting:** Sweden, 1973–2003.

**Participants:** All 324 sex-reassigned persons (191 male-to-females, 133 female-to-males) in Sweden, 1973–2003. Random population controls (10:1) were matched by birth year and birth sex or reassigned (final) sex, respectively.

**Main Outcome Measures:** Hazard ratios (HR) with 95% confidence intervals (CI) for mortality and psychiatric morbidity were obtained with Cox regression models, which were adjusted for immigrant status and psychiatric morbidity prior to sex reassignment (adjusted HR [aHR]).

**Results:** The overall mortality for sex-reassigned persons was higher during follow-up (aHR 2.8; 95% CI 1.8–4.3) than for controls of the same birth sex, particularly death from suicide (aHR 19.1; 95% CI 5.8–62.9). Sex-reassigned persons also had an increased risk for suicide attempts (aHR 4.9; 95% CI 2.9–8.5) and psychiatric inpatient care (aHR 2.8; 95% CI 2.0–3.9). Comparisons with controls matched on reassigned sex yielded similar results. Female-to-males, but not male-to-females, had a higher risk for criminal convictions than their respective birth sex controls.

**Conclusions:** Persons with transsexualism, after sex reassignment, have considerably higher risks for mortality, suicidal behaviour, and psychiatric morbidity than the general population. Our findings suggest that sex reassignment, although alleviating gender dysphoria, may not suffice as treatment for transsexualism, and should inspire improved psychiatric and somatic care after sex reassignment for this patient group.

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## Introduction

Transsexualism (ICD-10), [1] or gender identity disorder (DSM-IV), [2] is a condition in which a person's gender identity - the sense of being a man or a woman - contradicts his or her bodily sex characteristics. The individual experiences gender dysphoria and desires to live and be accepted as a member of the opposite sex.

The treatment for transsexualism includes removal of body hair, vocal training, and cross-sex hormonal treatment aimed at making the person's body as congruent with the opposite sex as possible to alleviate the gender dysphoria. Sex reassignment also involves the surgical removal of body parts to make external sexual characteristics resemble those of the opposite sex, so called sex reassignment/confirmation surgery (SRS). This is a unique

intervention not only in psychiatry but in all of medicine. The present form of sex reassignment has been practised for more than half a century and is the internationally recognized treatment to ease gender dysphoria in transsexual persons.[3,4]

Despite the long history of this treatment, however, outcome data regarding mortality and psychiatric morbidity are scant. With respect to suicide and deaths from other causes after sex reassignment, an early Swedish study followed 24 transsexual persons for an average of six years and reported one suicide.[5] A subsequent Swedish study recorded three suicides after sex reassignment surgery of 175 patients.[6] A recent Swedish follow-up study reported no suicides in 60 transsexual patients, but one death due to complications after the sex reassignment surgery.[7] A Danish study reported death by suicide in 3 out of 29 operated male-to-female transsexual persons followed for an average of six years.[8] By contrast, a Belgian study of 107 transsexual persons followed for 4–6 years found no suicides or deaths from other causes.[9] A large Dutch single-centre study ( $N=1,109$ ), focusing on adverse events following hormonal treatment, compared the outcome after cross-sex hormone treatment with national Dutch standardized mortality and morbidity rates and found no increased mortality, with the exception of death from suicide and AIDS in male-to-females 25–39 years of age.[10] The same research group concluded in a recent report that treatment with cross-sex hormones seems acceptably safe, but with the reservation that solid clinical data are missing.[11] A limitation with respect to the Dutch cohort is that the proportion of patients treated with cross-sex hormones who also had surgical sex-reassignment is not accounted for.[10]

Data is inconsistent with respect to psychiatric morbidity post sex reassignment. Although many studies have reported psychiatric and psychological improvement after hormonal and/or surgical treatment,[7,12,13,14,15,16] other have reported on regrets,[17] psychiatric morbidity, and suicide attempts after SRS.[9,18] A recent systematic review and meta-analysis concluded that approximately 80% reported subjective improvement in terms of gender dysphoria, quality of life, and psychological symptoms, but also that there are studies reporting high psychiatric morbidity and suicide rates after sex reassignment.[19] The authors concluded though that the evidence base for sex reassignment “is of very low quality due to the serious methodological limitations of included studies.”

The methodological shortcomings have many reasons. First, the nature of sex reassignment precludes double blind randomized controlled studies of the result. Second, transsexualism is rare [20] and many follow-ups are hampered by small numbers of subjects.[5,8,21,22,23,24,25,26,27,28] Third, many sex reassigned persons decline to participate in follow-up studies, or relocate after surgery, resulting in high drop-out rates and consequent selection bias.[6,9,12,21,24,28,29,30] Fourth, several follow-up studies are hampered by limited follow-up periods.[7,9,21,22,26,30] Taken together, these limitations preclude solid and generalisable conclusions. A long-term population-based controlled study is one way to address these methodological shortcomings.

Here, we assessed mortality, psychiatric morbidity, and psychosocial integration expressed in criminal behaviour after sex reassignment in transsexual persons, in a total population cohort study with long-term follow-up information obtained from Swedish registers. The cohort was compared with randomly selected population controls matched for age and gender. We adjusted for premorbid differences regarding psychiatric morbidity and immigrant status. This study design sheds new light on transsexual persons' health after sex reassignment. It does not, however, address whether sex reassignment is an effective treatment or not.

## Methods

### National registers

The study population was identified by the linkage of several Swedish national registers, which contained a total of 13.8 million unique individuals. The Hospital Discharge Register (HDR, held by the National Board of Health and Welfare) contains discharge diagnoses, up to seven contributory diagnoses, external causes of morbidity or mortality, surgical procedure codes, and discharge date. Discharge diagnoses are coded according to the 8<sup>th</sup> (1969–1986), 9<sup>th</sup> (1987–1996), and 10<sup>th</sup> editions (1997–) of the International Classification of Diseases (ICD). The register covers virtually all psychiatric inpatient episodes in Sweden since 1973. Discharges that occurred up to 31 December 2003 were included. Surgical procedure codes could not be used for this study due to the lack of a specific code for sex reassignment surgery. The Total Population Register (TPR, held by Statistics Sweden) is comprised of data about the entire Swedish population. Through linkage with the Total Population Register it was possible to identify birth date and birth gender for all study subjects. The register is updated every year and gender information was available up to 2004/2005. The Medical Birth Register (MBR) was established in 1973 and contains birth data, including gender of the child at birth. National censuses based on mandatory self-report questionnaires completed by all adult citizens in 1960, 1970, 1980, and 1990 provided information on individuals, households, and dwellings, including gender, living area, and highest educational level. Complete migration data, including country of birth for immigrants for 1969–2003, were obtained from the TPR. In addition to educational information from the censuses, we also obtained highest educational level data for 1990 and 2000 from the Register of Education. The Cause of Death Register (CDR, Statistics Sweden) records all deaths in Sweden since 1952 and provided information on date of death and causes of death. Death events occurring up to 31 December 2003 are included in the study. The Crime Register (held by the National Council of Crime Prevention) provided information regarding crime type and date on all criminal convictions in Sweden during the period 1973–2004. Attempted and aggravated forms of all offences were also included. All crimes in Sweden are registered regardless of insanity at the time of perpetration; for example, for individuals who suffered from psychosis at the time of the offence. Moreover, conviction data include individuals who received custodial or non-custodial sentences and cases where the prosecutor decided to caution or fine without court proceedings. Finally, Sweden does not differ considerably from other members of the European Union regarding rates of violent crime and their resolution.[31]

### Study population, identification of sex-reassigned persons (exposure assessment)

The study was designed as a population-based matched cohort study. We used the individual national registration number, assigned to all Swedish residents, including immigrants on arrival, as the primary key through all linkages. The registration number consists of 10 digits; the first six provide information of the birth date, whereas the ninth digit indicates the gender. In Sweden, a person presenting with gender dysphoria is referred to one of six specialised gender teams that evaluate and treat patients principally according to international consensus guidelines: Standards of Care.[3] With a medical certificate, the person applies to the National Board of Health and Welfare to receive permission for sex reassignment surgery and a change of legal sex status. A new national registration number signifying the new gender is assigned after sex reassignment surgery. The National



Board of Health and Welfare maintains a link between old and new national registration numbers, making it possible to follow individuals undergoing sex reassignment across registers and over time. Hence, sex reassignment surgery in Sweden requires (i) a transsexualism diagnosis and (ii) permission from the National Board of Health and Welfare.

A person was defined as exposed to sex reassignment surgery if two criteria were met: (i) at least one inpatient diagnosis of gender identity disorder diagnosis without concomitant psychiatric diagnoses in the Hospital Discharge Register, and (ii) at least one discrepancy between gender variables in the Medical Birth Register (from 1973 and onwards) or the National Censuses from 1960, 1970, 1980, or 1990 and the latest gender designation in the Total Population Register. The first criterion was employed to capture the hospitalization for sex reassignment surgery that serves to secure the diagnosis and provide a time point for sex reassignment surgery; the plastic surgeons namely record the reason for sex reassignment surgery, i.e., transsexualism, but not any co-occurring psychiatric morbidity. The second criterion was used to ensure that the person went through all steps in sex-reassignment and also changed sex legally.

The date of sex reassignment (start of follow-up) was defined as the first occurrence of a gender identity disorder diagnosis, without any other concomitant psychiatric disorder, in the Hospital Discharge Register after the patient changed sex status (any discordance in sex designation across the Censuses, Medical Birth, and Total Population registers). If this information was missing, we used instead the closest date in the Hospital Discharge Register on which the patient was diagnosed with gender identity disorder without concomitant psychiatric disorder prior to change in sex status. The reason for prioritizing the use of a gender identity disorder diagnosis *after* changed sex status over *before* was to avoid overestimating person-years at risk of sex-reassigned person.

Using these criteria, a total of 804 patients with gender identity disorder were identified, whereof 324 displayed a shift in the gender variable during the period 1973–2003. The 480 persons that did not shift gender variable comprise persons who either did not apply, or were not approved, for sex reassignment surgery. Moreover, the ICD 9 code 302 is a non specific code for sexual disorders. Hence, this group might also comprise persons that were hospitalized for sexual disorders other than transsexualism. Therefore, they were omitted from further analyses. Of the remaining 324 persons, 288 were identified with the gender identity diagnosis *after* and 36 *before* change of sex status. Out of the 288 persons identified *after* changed sex status, 185 could also be identified *before* change in sex status. The median time lag between the hospitalization *before* and *after* sex change for these 185 persons was 0.96 years (mean 2.2 years, SD 3.3).

Gender identity disorder was coded according to ICD-8: 302.3 (transsexualism) and 302.9 (sexual deviation NOS); ICD-9: 302 (overall code for sexual deviations and disorders, more specific codes were not available in ICD-9); and ICD-10: F64.0 (transsexualism), F64.1 (dual-role transvestism), F64.8 (other gender identity disorder), and F64.9 (gender identity disorder NOS). Other psychiatric disorders were coded as ICD-8: 290-301 and 303-315; ICD-9: 290-301 and 303-319; and ICD-10: F00-F63 as well as F65-F99.

#### Identification of population-based controls (unexposed group)

For each exposed person ( $N = 324$ ), we randomly selected 10 unexposed controls. 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 according to the Hospital Discharge Register. Control persons were matched by sex and birth year and had to be alive and residing in Sweden at the estimated sex reassignment date of the case person. To study possible gender-specific effects on outcomes of interest, we used two different control groups: one with the same sex as the case individual at birth (birth sex matching) and the other with the sex that the case individual had been reassigned to (final sex matching).

#### Outcome measures

We studied mortality, psychiatric morbidity, accidents, and crime following sex reassignment. More specifically, we investigated: (1) all-cause mortality, (2) death by definite/uncertain suicide, (3) death by cardiovascular disease, and (4) death by tumour. Morbidity included (5) any psychiatric disorder (gender identity disorders excluded), (6) alcohol/drug misuse and dependence, (7) definite/uncertain suicide attempt, and (8) accidents. Finally, we addressed court convictions for (9) any criminal offence and (10) any violent offence. Each individual could contribute with several outcomes, but only one event per outcome. Causes of death (Cause of Death Registry from 1952 and onwards) were defined according to ICD as suicide (ICD-8 and ICD-9 codes E950-E959 and E980-E989, ICD-10 codes X60-X84 and Y10-Y34); cardiovascular disease (ICD-8 codes 390-458, ICD-9 codes 390-459, ICD-10 codes I00-I99); neoplasms (ICD-8 and ICD-9 codes 140-239, ICD-10 codes C00-D48), any psychiatric disorder (gender identity disorders excluded); (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/drug abuse and dependence (ICD-8 codes 303-304, ICD-9 codes 303-305 (tobacco use disorder excluded), ICD-10 codes F10-F16 and F18-F19 (x5 excluded)); and accidents (ICD-8 and ICD-9 codes E800-E929, ICD-10 codes V01-X59).

Any criminal conviction during follow-up was counted; specifically, violent crime was defined as homicide and attempted homicide, aggravated assault and assault, robbery, threatening behaviour, harassment, arson, or any sexual offense.[32]

#### Covariates

Severe psychiatric morbidity was defined as inpatient care according to 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, defined as individuals born abroad, was obtained from the Total Population Register. All outcome/covariate variables were dichotomized (i.e., affected or unaffected) and without missing values.

#### 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 (31 December 2003), whichever came first. The association between exposure (sex reassignment) and outcome (mortality, morbidity, crime) was measured by hazard ratios (HR) with 95% CIs, taking follow-up time into account. HRs were estimated from Cox proportional hazard regression models, stratified on matched sets (1:10) to account for the matching by sex, age, and calendar time (birth year). We present crude HRs (though adjusted for sex and age through matching) and confounder-adjusted HRs [aHRs] 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 [18,33] and different prevalence across cases and controls (Table 1).

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 0.05 (all tests were two-sided). All outcome/covariate variables were without missing values, since they are generated from register data, which are either present (affected) or missing (unaffected). The data were analysed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

### Ethics

The data linking of national registers required for this study was approved by the IRB at Karolinska Institutet, Stockholm. All data were analyzed anonymously; therefore, informed consent for each individual was neither necessary nor possible.

### Results

We identified 324 transsexual persons (exposed cohort) who underwent sex reassignment surgery and were assigned a new legal sex between 1973 and 2003. These constituted the sex-reassigned (exposed) group. Fifty-nine percent ( $N = 191$ ) of sex-reassigned persons were male-to-females and 41% ( $N = 133$ ) female-to-males, yielding a sex ratio of 1.4:1 (Table 1).

The average follow-up time for all-cause mortality was 11.4 (median 9.1) years. The average follow-up time for the risk of being hospitalized for any psychiatric disorder was 10.4 (median 8.1).

### Characteristics prior to sex reassignment

Table 1 displays demographic characteristics of sex-reassigned and control persons prior to study entry (sex reassignment). There were no substantial differences between female-to-males and male-to-females regarding measured baseline characteristics. Immigrant status was twice as common among transsexual individuals compared to controls, living in an urban area somewhat more common, and higher education about equally prevalent. Transsexual individuals had been hospitalized for psychiatric morbidity other than gender identity disorder prior to sex reassignment about four times more often than controls. To adjust for these baseline discrepancies, hazard ratios adjusted for immigrant status and psychiatric morbidity prior to baseline are presented for all outcomes [aHRs].

### Mortality

Table 2 describes the risks for selected outcomes during follow-up among sex-reassigned persons, compared to same-age controls of the same birth sex. Sex-reassigned transsexual persons of both genders had approximately a three times higher risk of all-cause mortality than controls, also after adjustment for covariates. Table 2

**Table 1. Baseline characteristics among sex-reassigned subjects in Sweden ( $N = 324$ ) and population controls matched for birth year and sex.**

Characteristic at baseline	Sex-reassigned subjects ( $N = 324$ )	Birth-sex matched controls ( $N = 3,240$ )	Final-sex matched controls ( $N = 3,240$ )
<b>Gender</b>			
Female at birth, male after sex change	133 (41%)	1,330 (41%)	1,330 (41%)
Male at birth, female after sex change	191 (59%)	1,910 (59%)	1,910 (59%)
<b>Average age at study entry [years] (SD, min-max)</b>			
Female at birth, male after sex change	33.3 (8.7, 20–62)	33.3 (8.7, 20–62)	33.3 (8.7, 20–62)
Male at birth, female after sex change	36.3 (10.1, 21–69)	36.3 (10.1, 21–69)	36.3 (10.1, 21–69)
Both genders	35.1 (9.7, 20–69)	35.1 (9.7, 20–69)	35.1 (9.7, 20–69)
<b>Immigrant status</b>			
Female at birth, male after sex change	28 (21%)	118 (9%)	100 (8%)
Male at birth, female after sex change	42 (22%)	176 (9%)	164 (9%)
Both genders	70 (22%)	294 (9%)	264 (8%)
<b>Less than 10 years of schooling prior to entry vs. 10 years or more</b>			
Females at birth, males after sex change	49 (44%); 62 (56%)	414 (37%); 714 (63%)	407 (36%); 713 (64%)
Males at birth, females after sex change	61 (41%); 89 (59%)	665 (40%); 1,011 (60%)	595 (35%); 1,091 (65%)
All individuals with data	110 (42%); 151 (58%)	1,079 (38%); 1,725 (62%)	1,002 (36%); 1,804 (64%)
<b>Psychiatric morbidity* prior to study entry</b>			
Female at birth, male after sex change	22 (17%)	47 (4%)	42 (3%)
Male at birth, female after sex change	36 (19%)	76 (4%)	72 (4%)
Both genders	58 (18%)	123 (4%)	114 (4%)
<b>Rural [vs. urban] living area prior to entry</b>			
Female at birth, male after sex change	13 (10%)	180 (14%)	195 (15%)
Male at birth, female after sex change	20 (10%)	319 (17%)	272 (14%)
Both genders	33 (10%)	499 (15%)	467 (14%)

**Notes:**

\*Hospitalizations for gender identity disorder were not included.  
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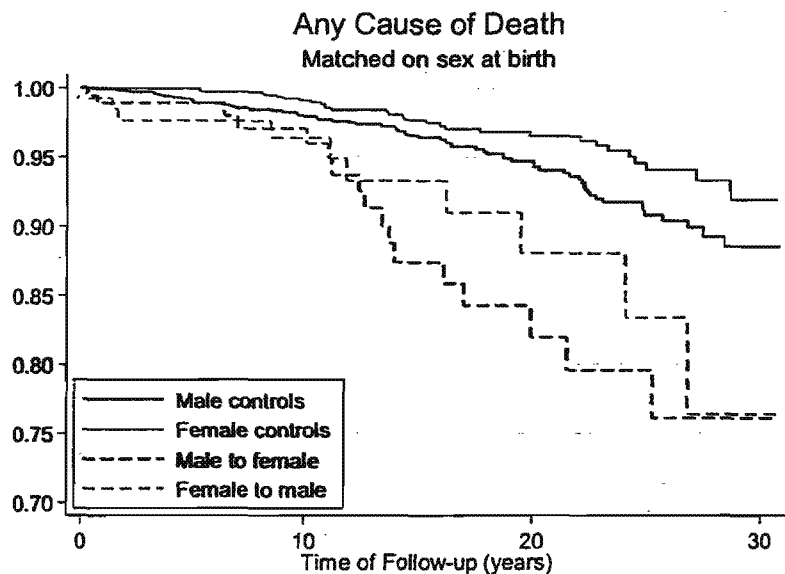
**Table 2. Risk of various outcomes among sex-reassigned subjects in Sweden (N = 324) compared to population controls matched for birth year and birth sex.**

	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* hazard ratio (95% CI) 1973–2003	Adjusted* hazard ratio (95% CI) 1973–1988	Adjusted* 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)
Death 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
Death 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
Death 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 hospitalisation‡	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 misuse	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

**Notes:**  
 \*Adjusted for psychiatric morbidity prior to baseline and immigrant status.  
 †Hospitalisations for gender identity disorder were excluded.  
 N/A Not applicable due to sparse data.  
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separately lists the outcomes depending on when sex reassignment was performed: during the period 1973–1988 or 1989–2003. Even though the overall mortality was increased across both time periods, it did not reach statistical significance for the period 1989–2003. The Kaplan-Meier curve (Figure 1) suggests that survival of transsexual persons started to diverge from that of matched controls after about 10 years of follow-up. The cause-specific mortality from

suicide was much higher in sex-reassigned persons, compared to matched controls. Mortality due to cardiovascular disease was moderately increased among the sex-reassigned, whereas the numerically increased risk for malignancies was borderline statistically significant. The malignancies were lung cancer (N = 3), tongue cancer (N = 1), pharyngeal cancer (N = 1), pancreas cancer (N = 1), liver cancer (N = 1), and unknown origin (N = 1).



**Figure 1. Death from any cause as a function of time after sex reassignment among 324 transsexual persons in Sweden (male-to-female: N = 191, female-to-male: N = 133), and population controls matched on birth year.**  
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### Psychiatric morbidity, substance misuse, and accidents

Sex-reassigned persons had a higher risk of inpatient care for a psychiatric disorder other than gender identity disorder than controls matched on birth year and birth sex (Table 2). This held after adjustment for prior psychiatric morbidity, and was true regardless of whether sex reassignment occurred before or after 1989. In line with the increased mortality from suicide, sex-reassigned individuals were also at a higher risk for suicide attempts, though this was not statistically significant for the time period 1989–2003. The risks of being hospitalised for substance misuse or accidents were not significantly increased after adjusting for covariates (Table 2).

### Crime rate

Transsexual individuals were at increased risk of being convicted for any crime or violent crime after sex reassignment (Table 2); this was, however, only significant in the group who underwent sex reassignment before 1989.

### Gender differences

Comparisons of female-to-males and male-to-females, although hampered by low statistical power and associated wide confidence intervals, suggested mostly similar risks for adverse outcomes (Tables S1 and S2). However, violence against self (suicidal behaviour) and others ([violent] crime) constituted important exceptions. First, male-to-females had significantly increased risks for suicide attempts compared to both female (aHR 9.3; 95% CI 4.4–19.9) and male (aHR 10.4; 95% CI 4.9–22.1) controls. By contrast, female-to-males had significantly increased risk of suicide attempts only compared to male controls (aHR 6.8; 95% CI 2.1–21.6) but not compared to female controls (aHR 1.9; 95% CI 0.7–4.8). This suggests that male-to-females are at higher risk for suicide attempts after sex reassignment, whereas female-to-males maintain a female pattern of suicide attempts after sex reassignment (Tables S1 and S2).

Second, regarding any crime, male-to-females had a significantly increased risk for crime compared to female controls (aHR 6.6; 95% CI 4.1–10.8) but not compared to males (aHR 0.8; 95% CI 0.5–1.2). This indicates that they retained a male pattern regarding criminality. The same was true regarding violent crime. By contrast, female-to-males had higher crime rates than female controls (aHR 4.1; 95% CI 2.5–6.9) but did not differ from male controls. This indicates a shift to a male pattern regarding criminality and that sex reassignment is coupled to increased crime rate in female-to-males. The same was true regarding violent crime.

## Discussion

### Principal findings and comparison with previous research

We report on the first nationwide population-based, long-term follow-up of sex-reassigned transsexual persons. We compared our cohort with randomly selected population controls matched for age and gender. The most striking result was the high mortality rate in both male-to-females and female-to-males, compared to the general population. This contrasts with previous reports (with one exception [8]) that did not find an increased mortality rate after sex reassignment, or only noted an increased risk in certain subgroups. [7,9,10,11] Previous clinical studies might have been biased since people who regard their sex reassignment as a failure are more likely to be lost to follow-up. Likewise, it is cumbersome to track deceased persons in clinical follow-up studies. Hence, population-based register studies like the present are needed to improve representativity. [19,34]

The poorer outcome in the present study might also be explained by longer follow-up period (median >10 years) compared to previous studies. In support of this notion, the survival curve (Figure 1) suggests increased mortality from ten years after sex reassignment and onwards. In accordance, the overall mortality rate was only significantly increased for the group operated before 1989. However, the latter might also be explained by improved health care for transsexual persons during 1990s, along with altered societal attitudes towards persons with different gender expressions. [35]

Mortality due to cardiovascular disease was significantly increased among sex reassigned individuals, albeit these results should be interpreted with caution due to the low number of events. This contrasts, however, a Dutch follow-up study that reported no increased risk for cardiovascular events. [10,11] A recent meta-analysis concluded, however, that data on cardiovascular outcome after cross-sex steroid use are sparse, inconclusive, and of very low quality. [34]

With respect to neoplasms, prolonged hormonal treatment might increase the risk for malignancies, [36] but no previous study has tested this possibility. Our data suggested that the cause-specific risk of death from neoplasms was increased about twice (borderline statistical significance). These malignancies (see Results), however, are unlikely to be related to cross-hormonal treatment.

There might be other explanations to increased cardiovascular death and malignancies. Smoking was in one study reported in almost 50% by the male-to-females and almost 20% by female-to-males. [9] It is also possible that transsexual persons avoid the health care system due to a presumed risk of being discriminated.

Mortality from suicide was strikingly high among sex-reassigned persons, also after adjustment for prior psychiatric morbidity. In line with this, sex-reassigned persons were at increased risk for suicide attempts. Previous reports [6,8,10,11] suggest that transsexualism is a strong risk factor for suicide, also after sex reassignment, and our long-term findings support the need for continued psychiatric follow-up for persons at risk to prevent this.

Inpatient care for psychiatric disorders was significantly more common among sex-reassigned persons than among matched controls, both before and after sex reassignment. It is generally accepted that transsexuals have more psychiatric ill-health than the general population prior to the sex reassignment. [18,21,22,33] It should therefore come as no surprise that studies have found high rates of depression, [9] and low quality of life [16,25] also after sex reassignment. Notably, however, in this study the increased risk for psychiatric hospitalisation persisted even after adjusting for psychiatric hospitalisation prior to sex reassignment. This suggests that even though sex reassignment alleviates gender dysphoria, there is a need to identify and treat co-occurring psychiatric morbidity in transsexual persons not only before but also after sex reassignment.

Criminal activity, particularly violent crime, is much more common among men than women in the general population. A previous study of all applications for sex reassignment in Sweden up to 1992 found that 9.7% of male-to-female and 6.1% of female-to-male applicants had been prosecuted for a crime. [33] Crime after sex reassignment, however, has not previously been studied. In this study, male-to-female individuals had a higher risk for criminal convictions compared to female controls but not compared to male controls. This suggests that the sex reassignment procedure neither increased nor decreased the risk for criminal offending in male-to-females. By contrast, female-to-males were at a higher risk for criminal convictions compared to female controls and did not differ from male controls, which suggests increased crime proneness in female-to-males after sex reassignment.

### Strengths and limitations of the study

Strengths of this study include nationwide representativity over more than 30 years, extensive follow-up time, and minimal loss to follow-up. Many previous studies suffer from low outcome ascertainment,[6,9,21,29] whereas this study has captured almost the entire population of sex-reassigned transsexual individuals in Sweden from 1973–2003. Moreover, previous outcome studies have mixed pre-operative and post-operative transsexual persons,[22,37] while we included only post-operative transsexual persons that also legally changed sex. Finally, whereas previous studies either lack a control group or use standardised mortality rates or standardised incidence rates as comparisons,[9,10,11] we selected random population controls matched by birth year, and either birth or final sex.

Given the nature of sex reassignment, a double blind randomized controlled study of the result after sex reassignment is not feasible. We therefore have to rely on other study designs. For the purpose of evaluating whether sex reassignment is an effective treatment for gender dysphoria, it is reasonable to compare reported gender dysphoria pre and post treatment. Such studies have been conducted either prospectively[7,12] or retrospectively,[5,6,9,22,25,26,29,38] and suggest that sex reassignment of transsexual persons improves quality of life and gender dysphoria. The limitation is of course that the treatment has not been assigned randomly and has not been carried out blindly.

For the purpose of evaluating the safety of sex reassignment in terms of morbidity and mortality, however, it is reasonable to compare sex reassigned persons with matched population controls. The caveat with this design is that transsexual persons before sex reassignment might differ from healthy controls (although this bias can be statistically corrected for by adjusting for baseline differences). It is therefore important to note that the current study is only informative with respect to transsexuals persons health after sex reassignment; no inferences can be drawn as to the effectiveness of sex reassignment as a treatment for transsexualism. In other words, the results should not be interpreted such as sex reassignment *per se* increases morbidity and mortality. Things might have been even worse without sex reassignment. As an analogy, similar studies have found increased somatic morbidity, suicide rate, and overall mortality for patients treated for bipolar disorder and schizophrenia.[39,40] This is important information, but it does not follow that mood stabilizing treatment or antipsychotic treatment is the culprit.

Other facets to consider are first that this study reflects the outcome of psychiatric and somatic treatment for transsexualism provided in Sweden during the 1970s and 1980s. Since then, treatment has evolved with improved sex reassignment surgery, refined hormonal treatment,[11,41] and more attention to psychosocial care that might have improved the outcome. Second, transsexualism is a rare condition and Sweden is a small country (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* prevalences was inevitable. However, there is no reason to believe that this would change the *relative* risks for psychiatric morbidity unless sex-reassigned transsexual individuals were more likely than matched controls to be admitted to hospital for any given psychiatric condition.

Finally, to estimate start of follow-up, we prioritized using the date of a gender identity disorder diagnosis *after* changed sex status over *before* changed sex status, in order to avoid overestimating person-years at risk after sex-reassignment. This means that adverse outcomes might have been underestimated. However, given that the median time lag between the hospitalization before and after change of sex status was less than a year (see Methods), this maneuver is unlikely to have influenced the results significantly. Moreover, all deaths will be recorded regardless of this exercise and mortality hence correctly estimated.

### Conclusion

This study found substantially higher rates of overall mortality, death from cardiovascular disease and suicide, suicide attempts, and psychiatric hospitalisations in sex-reassigned transsexual individuals compared to a healthy control population. This highlights that post surgical transsexuals are a risk group that need long-term psychiatric and somatic follow-up. Even though surgery and hormonal therapy alleviates gender dysphoria, it is apparently not sufficient to remedy the high rates of morbidity and mortality found among transsexual persons. Improved care for the transsexual group after the sex reassignment should therefore be considered.

### Supporting Information

**Table S1 Risk of various outcomes in sex-reassigned persons in Sweden compared to population controls matched for birth year and birth sex.**  
(DOCX)

**Table S2 Risk of various outcomes in sex-reassigned persons in Sweden compared to controls matched for birth year and final sex.**  
(DOCX)

### Author Contributions

Conceived and designed the experiments: CD PL AJ NL ML. Performed the experiments: MB AJ. Analyzed the data: CD PL MB AJ NL ML. Contributed reagents/materials/analysis tools: PL NL AJ. Wrote the paper: CD PL MB AJ NL ML.

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