IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF FLORIDA
TALLAHASSEE DIVISION

AUGUST DEKKER, et al., *Plaintiffs*, v. JASON WEIDA, et al., *Defendants*.	Case No. 4:22-cv-00325-RH-MAF

EXPERT REPORT OF MICHAEL BIGGS, Ph.D.

1. I have been retained by counsel for the Florida Agency for Health Care Administration in defence of revisions to Rule 59G-1.050, Florida Administrative Code (*Dekker et al. v. Weida et al.*, Case No. 4:22-cv-00325-RH-MAF). I have been asked by counsel to summarize my knowledge and opinions on gender dysphoria in adolescents, focusing on the use of puberty blockers.

2. I have contributed to the following legal cases:

   a. Expert witness statement for Keira Bell and Mrs A in *Keira Bell and Mrs A v Tavistock NHS Trust,* Her Majesty's High Court of Justice in England, 2020, [2020] EWHC 3274 (Admin).

   b. Expert witness statement for [name suppressed], Australian Family Court, 2022.

3. A list of my publications is included in my curriculum vitae, which is attached as Attachment 1. My publications related to gender dysphoria are included as Attachments 2 through 5.

4. I am being compensated for my time in preparing this report at an hourly rate of $400/hour. My compensation is in no way contingent on the conclusions reached as a result of my analysis.

Background

5. With a PhD degree from Harvard University, I conduct research on social movements by compiling original quantitative data and using statistical methods.

Around 2017 my interest was piqued by the rapid growth in the number of children identifying as transgender, throughout the Western world. Three graduate students told me not to analyze this phenomenon sociologically and to educate myself in the correct way of thinking. After reading the scientific literature, I became increasingly concerned about the lack of robust evidence on endocrinological and surgical interventions.

6. I have conducted original research on the use of Gonadotropin-Releasing Hormone agonist or analogue (GnRHa) to block the development of puberty. I have written on the invention of the Dutch protocol in the 1990s (Biggs 2022b) and on the initial British experiment with this protocol in the 2010s (Biggs 2019b). I was the first to call on the Tavistock and Portman NHS Foundation Trust's Gender Identity Development Service (GIDS) to publish the results of its experiment (Tominey and Walsh 2019), and I was the first to publish preliminary results from the experiment (Biggs 2020a). Provoked by the poor quality of data and analysis in this field of medicine, I have published on the effects of puberty suppression on psychological functioning (Biggs 2019a), on suicidality (Biggs 2020b), and on bone density (Biggs 2021), as well as on the suicide rate of transgender adolescents (Biggs 2022a). This work has appeared in leading psychology and medical journals: *Archives of Sexual Behavior*, *Journal of Sex and Marital Therapy*, *Journal of Sexual Medicine*, and *Journal of Pediatric Endocrinology and*

Metabolism. My articles have been published in the top disciplinary journals including *American Sociological Review*, *American Journal of Sociology*, *Social Forces*, *European Sociological Review*, and *British Journal of Sociology*.

Puberty Suppression as a Treatment for Gender Dysphoria

7. In the nomenclature of transgender medicine, "puberty blockers" denote GnRHa drugs which stop the production of sex hormones. Drugs in this class used in North America include and leuprorelin (branded Lupron) and histrelin acetate (branded Supprelin LA or Vantas). GnRHa has never been licensed to treat gender dysphoria anywhere in the world. The justification for this application comes by analogy with its licensed use to treat precocious puberty—when puberty commences before the age of 7 (approximately) in girls or 9 in boys. That treatment involves delaying a puberty that arrives abnormally early so that the child can undergo puberty at the normal age, whereas puberty suppression for gender dysphoria entails stopping normal puberty in order to prepare the child for taking hormones of the opposite sex.

8. Dutch clinicians started using GnRHa to suppress puberty in children suffering from gender dysphoria—who they designated as "juvenile transsexuals" (Gooren and Delemarre-van de Waal 1996)—in the 1990s. The Dutch protocol had three stages (Delemarre-van de Waal and Cohen-Kettenis 2006). GnRHa would be given from the age of 12, once the child had reached Tanner Stage 2: for girls by

budding breasts and for boys by growing testicles. Cross-sex hormones would be administered from 16, and surgeries would commence at 18.

9. Puberty suppression as a treatment for gender dysphoria was never tested in any randomized clinical trial. Nor were there any preliminary experiments on non-human animals. Only two decades after this treatment was first used on children were any experiments conducted on sheep and mice (Hough, Bellingham, Haraldsen, McLaughlin, Rennie, et al. 2017; Hough, Bellingham, Haraldsen, McLaughlin, Robinson, et al. 2017; Anacker et al. 2021). The Dutch clinicians published outcomes from a longitudinal study of the first cohort of 70 children whose puberty was suppressed (de Vries et al. 2011; 2014). About half the psychological measures showed improvement. The reported improvement in gender dysphoria is flawed because the researchers switched the questionnaires used to construct the measure. A male who wanted to become a woman was given the male version at baseline and then the female version at follow-up, including irrelevant questions such as about menstruation (Levine, Abbruzzese, and Mason 2022). Notably, one teenager died of necrotizing fasciitis during vaginoplasty. This death was a consequence of puberty suppression: the patient's penis, prevented from developing normally, was too small for the regular vaginoplasty and so surgery was attempted with a portion of the intestine, which became infected

(Negenborn et al. 2017). In a cohort of healthy teenagers, a death rate exceeding 1% is alarming.

10. This Dutch cohort have not been followed up since their early twenties, just after surgery. Only one patient—the very first to receive puberty suppression for gender dysphoria—has been followed up in the long term. At the age of 35, he was depressed. Due to "shame about his genital appearance and his feelings of inadequacy in sexual matters," he could not sustain a romantic relationship with a girlfriend (Cohen-Kettenis et al. 2011, 845). The clinicians concluded optimistically that "the negative side effects are limited" (Cohen-Kettenis et al. 2011, 843).

11. While gender clinics in many other countries adopted the Dutch protocol from the late 2000s, they either did not collect data on outcomes or decided not to publish it. The GIDS started puberty suppression as an experiment in 2011, involving 44 children aged 12 to 15 (Viner et al. 2010). Before the last subject had been recruited, it was pronounced a success by the Director of the GIDS and used to justify a new policy of lowering the age of puberty suppression: "Now we've done the study and the results thus far have been positive we've decided to continue with it" (Manning and Adams 2014). The lack of publication of the results led to my protracted campaign involving news media (e.g., Tominey and Walsh 2019), complaints to the NHS ethics committee (Health Research Authority

2019), and questions in Parliament (Blackwood of North Oxford 2019). The GIDS delayed publication until the day after the verdict was delivered in the judicial review launched by Keira Bell (Carmichael et al. 2020; 2021). The researchers acknowledge that puberty suppression, after two years, produced no positive effects. These results were significantly inferior to the Dutch results following puberty suppression (Biggs 2020a). The subjects of this experiment have not been followed up after cross-sex hormones; the GIDS admits that it loses track of its patients after the age of 18 (Butler et al. 2018). One of the subjects in the experiment appeared on Twitter (as @mediocredruid): she is deeply distressed by her treatment—GnRHa at 15 led to testosterone, double mastectomy, hysterectomy, vaginectomy, and metoidioplasty—and is now stuck in medical limbo, as the physical changes have been so extreme that she is unlikely to be able to pass as a woman.

12. In the United States, puberty suppression became widely adopted from 2008 onwards (Biggs 2020b). Dozens of children's gender clinics were established to tap into this new lucrative market. The National Institutes of Health awarded $5.7 million for a prospective longitudinal study of the effects of GnRHa and cross-sex hormones on children (Children's Hospital Los Angeles 2015). Subjects were recruited between 2016 and 2018 (Olson-Kennedy et al. 2019). Outcomes after two years on GnRHa were thus collected by 2020, but the researchers have only

published on the characteristics of the cohort *before* treatment (Chen et al. 2021; Lee et al. 2020) and on the respective merits of two brands of GnRHa (Olson-Kennedy et al. 2021). As in Britain, practitioners of gender medicine are curiously reluctant to publish the outcomes of puberty suppression for psychological functioning and gender dysphoria—even though those outcomes were the primary justification for the treatment.

The Association of Gender Dysphoria with Same-Sex Attraction and Autism Spectrum Conditions

13. Puberty suppression is founded on the assumption that a child suffering from gender dysphoria at age 12—or even younger, if Tanner stage 2 is reached earlier—is a "juvenile transsexual" whose destiny is fixed. This assumption was known to be false by the clinicians who invented the Dutch protocol, who initially recognized that "most GID [gender identity disorder, the precursor to gender dysphoria] children under 12 will not grow up to become transsexuals" (Cohen-Kettenis and van Goozen 1997, 246). "Prospective studies of GID boys show that this phenomenon is more closely related to later homosexuality than to later transsexualism" (Cohen-Kettenis and Gooren 1999, 319). One of the four studies cited is a famous study of "sissy boys" who were selected because they were thought to be "pretranssexuals"; after fifteen years, however, two thirds of the 44 had become bisexual or homosexual men and only one was contemplating

transsexuality (Green 1987). A representative longitudinal study of 14,000 children born in 1991–92 shows that those who as infants gravitated towards toys and activities typical of the opposite sex were far more likely by the age of 15 to grow up to be gay or lesbian (Li, Kung, and Hines 2017). All this evidence predates the promotion of transgenderism in healthcare and schools and on social media. The manifesto for the Dutch protocol fails to mention homosexuality and does not cite any of the studies of feminine boys (Delemarre-van de Waal and Cohen-Kettenis 2006). Of the first 70 adolescents referred to the Amsterdam clinic from 2000 to 2008 and given GnRHa, 62 were homosexual while only 1 was heterosexual (de Vries et al., 2011). The suspicion must be that at least some of these children could have grown up to be typical gays and lesbians, without requiring lifetime medical treatment and without loss of fertility and sexual function.

14. The overlap between gender dysphoria and autistic spectrum conditions (ASC) is well documented (Socialstyrelsen 2020; Warrier et al. 2020). "GD [gender dysphoria] and ASD [autism spectrum disorder, another term for ASC] were found to co-occur frequently—sometimes characterized by atypical presentation of GD, which makes a correct diagnosis and determination of treatment options for GD difficult" (van der Miesen, Hurley, and de Vries 2016, 70). Children on the autistic spectrum are more likely to face difficulties fitting in with their same-sex peers, which makes a transgender identity obviously appealing

as both an explanation and a solution. From a sample of over 700 referrals to the GIDS in 2012 and 2015, 14–15% were diagnosed with ASC (Morandini et al. 2021). This was more than ten times greater than the rate for students in England, 0.8%–1.1% (Department for Education 2012; 2015). The proportion among those subjected to GnRHa could be even higher. Out of the first 30 subjects enrolled in the GIDS experiment on puberty suppression, almost half had ASC traits: mid to moderate in 9 children, and severe in 5 (Gender Identity Development Service 2015).

The Risk of Suicide for Children Suffering from Gender Dysphoria

15. Surveys demonstrate that adolescents who identify as transgender are vulnerable to suicidal thoughts and self-harming behaviors (dickey and Budge 2020; Hatchel, Polanin, and Espelage 2021; Mann et al. 2019). In the United States, 15% of transgender students reported a suicide attempt requiring medical treatment in the last 12 months, compared to 3% of all students (Centers for Disease Control and Prevention 2018; Jackman et al. 2021; Johns et al. 2019). In another American survey, 41% of transgender students reported having attempted suicide during their lifetime, compared to 14% of all students (Toomey, Syvertsen, and Shramko 2018).

16. Respondents who report suicide attempts are not necessarily indicating an intent to die. One survey of the American population found that almost half the

respondents who reported attempting suicide subsequently stated that their action was a cry for help and not intended to be fatal (Nock and Kessler 2006). In two small samples of non-heterosexual youth, half the respondents who initially reported attempting suicide subsequently clarified that they went no further than imagining or planning it; for the remainder who did actually attempt suicide, their actions were usually not life-threatening. To an extent, then, "the reports were attempts to communicate the hardships of lives or to identify with a gay community" (Savin-Williams 2001). Such elaborate survey methods have not been used to study transgender populations, but there is anecdotal evidence for a disjuncture between self-harm and suicidal ideation on one hand and fatal suicide on the other. The pediatric endocrinologist who established the first clinic for transgender children in the United States stated that "the majority of self-harmful actions that I see in my clinic are not real suicide attempts and are not usually life threatening" (Spack 2009, 312).

17. Two published studies have reported suicide fatalities among transgender adolescents. Belgium's pediatric gender clinic provided counselling to 172 youth aged from 12 and 18 years, who had been referred between 2007 and 2016: 5 of them (2.9%) committed suicide (Van Cauwenberg, Dhondt, and Motmans 2021). The mean age of referral was 15, implying a mean duration of 3 years before

transition to an adult clinic, which translates to an annual suicide rate of 969 per 100,000. This is extraordinarily high.

18. At the Tavistock GIDS, which serves young people under 18 from England, Wales, and Northern Ireland, 4 patients were known or suspected to have died by suicide between 2010 and 2020. The clinic had referrals for approximately 15,000 patients in this period. To calculate the annual suicide rate, the total number of years spent by patients under the clinic's care is estimated at about 30,000. This yields an annual suicide rate of 13 per 100,000 (95% confidence interval: 4–34). Compared to the United Kingdom population of the same age and sexual composition, the suicide rate for patients at the GIDS was 5.5 times higher (Biggs 2022a). It is not clear what explains the enormous disparity in suicide rates at these two clinics; the Belgian rate is 70 times higher. The suicide rate at the GIDS is much closer to the rates for adults. Among 4,600 adults who received cross-sex hormones at the Amsterdam clinic between 1972 and 2018, the suicide rate (standardized for age and sex) was triple that of the Dutch population (de Blok et al. 2021). Among 3,000 adults who were diagnosed with gender dysphoria in England, the (unstandardized) suicide rate was 3–6 times that of the population (Jackson et al. 2023).

19. The elevated suicide rate of children who identify as transgender could be explained by some combination of gender dysphoria, accompanying psychological

conditions, and ensuing social disadvantages such as bullying. The association between ASC and gender dysphoria was pointed out above. Autism is known to increase the risk of suicide mortality, especially in females (Socialstyrelsen 2020; Kirby et al. 2019; Hirvikoski et al. 2016). To some extent, therefore, the elevated suicide rate for transgender youth compared to their peers reflects the higher incidence of ASC. The same holds for other psychiatric disorders associated with gender dysphoria (Dhejne et al. 2016).

20. The claim that puberty suppression reduces suicidality in children suffering from gender dysphoria is not implausible. Because the risk of suicide increases greatly from prepubescence to late adolescence, halting normal cognitive and emotional development with GnRHa could reduce the risk of suicide by preventing the child from maturing. As yet there is no evidence, however, that endocrinological interventions reduce the risk of suicide. At the GIDS from 2010 to 2020, there is no detectable difference between the suicide rate for patients on the waiting list and for patients who were being seen (Biggs 2022a). In the Belgian clinic which experienced the exceptionally high suicide rate. subsequent correspondence reveals that "suicide was related to many more (psychological) problems than their GD [gender dysphoria], and occurred mostly a few years after the start on hormonal treatment" (email from Gaia Van Cauwenberg to Avi Ring, 27 May 2022).

21. One study claims that puberty suppression reduced subsequent suicidality in adults (Turban et al. 2020). This finding derives from a nonrepresentative survey of transgender adults in the United States, which included 89 respondents who reported taking puberty blockers. Six measures of suicidality and three other measures of mental health and substance abuse were examined, but only one yielded a statistically significant association after controlling for other factors: the respondents who reported taking puberty blockers were less likely to have thought about killing themselves than were the respondents who reported wanting blockers but not obtaining them. This study has numerous serious flaws (Biggs 2020b). Most fundamentally, without information on the respondents' mental health during adolescence, the causal direction cannot be ascertained. The association could well be explained by clinicians refusing to prescribe GnRHa to adolescents with significant psychological problems, as indeed was then recommended by the Endocrine Society (Hembree et al. 2009). The study did not disclose the fact that one of its authors had been paid by Endo Pharmaceuticals, which manufactures a GnRHa drug (histrelin acetate under the brand Supprelin). At my insistence, the journal issued a correction to admit this conflict of interest (Pediatrics 2021).

22. There are anecdotal reports of children experiencing increased suicidal feelings after GnRHa. At the Leiden clinic, one teenager "stopped treatment because of an increase in mood problems and suicidal thoughts and confusion

attributed to GnRHa treatment" (Brik et al. 2020, 2614). One English teenager recalled that GnRHa led to suicidal feelings (Klotz 2022). The drugs used in Britain—Gonapeptyl® Depot and Decapeptyl® SR—carry warnings that depression is a common side effect, affecting between 1% and 10% of patients (Ferring Pharmaceuticals Ltd 2016), and "may be severe" (Ipsen Ltd 2017).

The Effect of Puberty Suppression on Mental Health

23. The first Dutch cohort of 70 children given GnRHa reported generally positive outcomes, by age 16, when they graduated to cross-sex hormones (de Vries et al. 2011). (The actual number of observations ranged from 41 to 57, depending on measure.) Psychological functioning improved, depressive symptoms declined, and behavioural and emotional problems decreased. Gender dysphoria, however, worsened for females. Using the same measures as the Dutch, the first GIDS cohort of 44 children reported no improvement in psychological functioning or gender dysphoria after two years (Carmichael et al. 2021). On almost all measures, the outcomes for the GIDS cohort were worse than for the Dutch cohort (Biggs 2022b). There was a misleading earlier article from the GIDS which claimed that puberty suppression improved psychological functioning (Costa et al. 2015). It had an extraordinarily high attrition rate—almost half the subjects vanished over 12 months, without explanation—and the claimed effect

was actually not statistically significant (Biggs 2019a). It nevertheless continues to be cited as credible evidence for the beneficial effects of puberty suppression.

24. According to a recent study from the Seattle Children's Gender Clinic, 69 youth aged 13 to 16 experienced dramatically reduced rates of depression and of self-harm or suicidal thoughts after 12 months on GnRHa or cross-sex hormones (Tordoff et al. 2022). (The authors unfortunately do not differentiate these two interventions.) In fact the data for these youth showed no change over time (Singal 2022). The false claim was derived from statistical comparison with youth from the clinic who had not received these endocrinological interventions, whose mental health worsened over time. But this comparison group numbered only 6 patients after 12 months. One obvious explanation is that the clinicians were following the World Professional Association of Transgender Health's recommendations against commencing medical intervention when an adolescent is experiencing an acute mental health crisis. (This is the same fallacy of causal inference that vitiated Turban et al.'s (2020) study of suicidality.)

25. A proper randomized control trial of the effect of suppressing puberty in mice using GnRHa demonstrated that it caused significantly higher levels of stress in males, and increased anxiety and despair-like behaviour in females (Anacker et al. 2021).

The Effect of Puberty Suppression on Bone Density

26. The Dutch pioneers warned at the outset that patients could "end with a decreased bone density, which is associated with a high risk of osteoporosis" (Delemarre-van de Waal and Cohen-Kettenis 2006, S134). The fact that GnRHa prevents the accrual of normal bone mass is well documented from Dutch and British studies (Klink et al. 2015; Schagen et al. 2020; Stoffers, de Vries, and Hannema 2019; Vlot et al. 2017; Joseph, Ting, and Butler 2019). In addition, children given GnRHa already have unusually low bone density, perhaps due to the high prevalence of eating disorders. The combined effect can be appreciated by looking at the proportion of adolescents who end up after treatment with severely low bone density, two standard deviations below the average—putting them at risk for osteoporosis. My reanalysis of 31 of the GIDS patients demonstrates that after two years on GnRHa, up to a third had reached this very low range, depending on the measure (hip or spine); only 2.3% of the population would be this low. Moreover, four patients (13%) had spine bone density over three standard deviations from the mean; only 0.13% of the population would be so extremely low (Biggs 2021).

27. Whether such abnormally low bone density has increased the risk of fractures is unknown because clinics apparently do not collect data on fractures. Anecdotally, a British female patient who started GnRHa at age 12 then

experienced four broken bones by the age of 16 (Bannerman 2019). A Swedish documentary highlighted the case of a female who was given GnRHa from age 11 to 15, and now suffers from severe osteoporosis, including continual skeletal pain (SVT 2021).

The Effect of Puberty Suppression on Sexual Function

28. When GnRHa is used to treat prostate cancer, one side effect is that "sexual desire, sexual interest and sexual intercourse were totally annulled" (Marumo, Baba, and Murai 1999, 19). This is why GnRHa is licensed to chemically castrate men who are sex offenders (Ho et al. 2012; Turner and Briken 2018). Clinicians who use GnRHa off-label to treat gender dysphoria have ignored its effects on sexuality. The Dutch studies, for example, included no measures for libido or capacity for orgasm (de Vries et al. 2011; 2014). The lead author recently described orgasm as "a very interesting and so far not studied question" (Klotz 2022). A Californian surgeon who has performed over 2,000 vaginoplasties (and who is also transgender) recently acknowledged that "every single child who was, or adolescent, who was truly blocked at Tanner Stage 2, has never experienced orgasm. I mean, it's really about zero" (Bowers 2022). This remark refers to males. The effects of puberty suppression at such an early stage on females is unknown.

The Effect of Puberty Suppression on Subsequent Medical Transition

29. Dutch clinicians initially promoted puberty suppression as providing space for therapeutic exploration of gender identity, without the pressure of the physical changes accompanying puberty (Delemarre-van de Waal and Cohen-Kettenis 2006). This was plausible, perhaps, though it was also plausible that stopping normal sexual and cognitive development would impede such exploration. As the Dutch clinicians admitted at the time, "none of the [54] patients who were selected for pubertal suppression has decided to stop taking GnRHa" (Delemarre-van de Waal and Cohen-Kettenis 2006, S136). It could have been argued that this was due to careful selection of a small number of adolescents for this experimental treatment.

30. Although the number of children subjected to puberty suppression has increased dramatically, they almost invariably continue to cross-sex hormones. Out of 333 children given GnRHa in the Amsterdam clinic to the end of 2015, 326 (98%) continued to cross-sex hormones (Wiepjes et al. 2018). Out of 133 children given GnRHa at the Leiden clinic in the Netherlands who attained the age of eligibility for cross-sex hormones, 128 (96%) continued (Brik et al. 2020). Out of 44 children enrolled in the GIDS experiment with GnRHa, 43 (98%) continued to cross-sex hormones (Carmichael et al. 2021). Out of 54 children given GnRHa by the Royal Children's Hospital Gender Service in Australia, 53 (98%) continued to

cross-sex hormones (Tollit et al. 2021). The suspicion is that puberty suppression reinforces gender dysphoria.

31. Given the fact that there are almost no cases of children ceasing GnRHa, the claim for reversibility is moot. The article that first proposed puberty suppression deemed it to be "fully reversible; in other words, no lasting undesired effects are to be expected" (Gooren and Delemarre-van de Waal 1996, 72). The phrasing acknowledged the lack of actual evidence. Suppressing puberty for just one month would have a negligible effect on a child's development, of course, but the Dutch protocol entails suppression for up to four years (from age 12 to 16). It is simply incredible to claim that suppressing puberty for many years would have no lasting effect if the child were to stop GnRHa and restart their natal sex hormones. The manifesto for the Dutch protocol admitted as much: "It is not clear yet how pubertal suppression will influence brain development" (Delemarre-van de Waal and Cohen-Kettenis 2006, S137). Randomized experiments with sheep now provide compelling evidence on this point: GnRHa impairs spatial memory, and this impairment remains after the treatment is stopped and puberty is restarted (Hough et al. 2017a; Hough et al. 2017b).

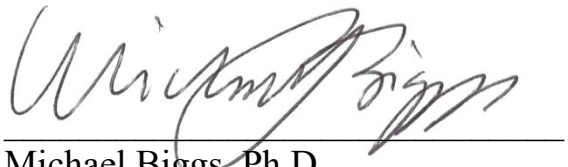
Recent Evaluations of Puberty Suppression by the English and Swedish Health Systems

32. NHS England commissioned a systematic evaluation of every study on puberty suppression published up to July 2020. From detailed analysis spanning

131 pages, it concluded: “The studies included in this evidence review are all small, uncontrolled observational studies, which are subject to bias and confounding, and all the results are of very low certainty using modified GRADE [Grading of Recommendations, Assessment, Development and Evaluations, a framework for summarizing medical evidence]. They all reported physical and mental health comorbidities and concomitant treatments very poorly” (National Institute for Clinical Excellence 2020, 23).

33. The Swedish National Board of Health and Welfare updated its recommendations in February 2022, based on a systematic review of the scientific evidence by the Agency for Health Technology Assessment and Assessment of Social Services (Statens beredning för medicinsk och social utvärdering 2022). It states that “the risks of puberty suppressing treatment with GnRH-analogues and gender-affirming [cross-sex] hormonal treatment currently outweigh the possible benefits, and that the treatments should be offered only in exceptional cases,” in part due to the “continued lack of reliable scientific evidence concerning the efficacy and the safety of both treatments” (Socialstyrelsen 2022, 3).

I declare, pursuant to 28 U.S.C. § 1746, under penalty of perjury that the foregoing is true and correct. Executed this 13th day of February, 2023.



Michael Biggs, Ph.D.

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Appended

1. Curriculum Vitae
2. Michael Biggs. 2020b. "Puberty Blockers and Suicidality in Adolescents Suffering from Gender Dysphoria." *Archives of Sexual Behavior* 49: 2227–29. https://doi.org/10.1007/s10508-020-01743-6.
3. Michael Biggs. 2021. "Revisiting the Effect of GnRH Analogue Treatment on Bone Mineral Density in Young Adolescents with Gender Dysphoria." *Journal of Pediatric Endocrinology and Metabolism* 34: 937–39. https://doi.org/10.1515/jpem-2021-0180.
4. Michael Biggs. 2022a. "Suicide by Clinic-Referred Transgender Adolescents in the United Kingdom." *Archives of Sexual Behavior* 51: 685–90. https://doi.org/10.1007/s10508-022-02287-7.
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Employment

2006-	Associate Professor (formerly Lecturer), Department of Sociology, University of Oxford; Fellow of St Cross College
2005-06	Lecturer, School of Sociology and Social Policy, Queen's University Belfast
2003-05	Assistant Professor, Department of Sociology, University of Illinois at Urbana-Champaign
2000-02	Junior Lecturer, Department of Sociology, University of Oxford

Education

2000	Doctor of Philosophy, Sociology, Harvard University: 'The Rise and Decline of a Mass Movement: American Workers and the Strike Wave of 1886' (Chair: Theda Skocpol)
1991	Bachelor of Arts—First Class Honours, History and Economic History, Victoria University of Wellington, New Zealand

Publications

'The Dutch Protocol for Juvenile Transsexuals: Origins and Evidence', *Journal of Sex and Marital Therapy*, 2022; DOI: 10.1080/0092623X.2022.2121238 (Stata program provided as DOI 10.7910/DVN/QPRCR1)

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‘Protest Campaigns and Movement Success: Desegregating the U.S. South in the Early 1960s’ (with Kenneth T. Andrews), *American Sociological Review*, vol. 80, no. 2, 2015, pp. 416-43; DOI 10.1177/0003122415574328 (data provided as ICPSR 35630)

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‘Explaining Membership in the British National Party: A Multilevel Analysis of Contact and Threat’ (with Steven Knauss), *European Sociological Review*, vol. 28, no. 5, 2012, pp. 633-46

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Under review

‘Gender Identity in the 2021 Census of England and Wales: Implausible Results’

‘The Technology of Puberty Suppression’, *Sex and Gender Identity: A Reader*, ed. Alice Sullivan and Selina Todd, under contract with Routledge, manuscript submitted August 2022

‘How Protesting Depends on Peers: U.S. Students in the 1960s’, revise and resubmit

Conference presentations

Annual meeting of the American Sociological Association, 1995, 1997, 1999, 2002, 2003, 2005, 2006 (invited, thematic session), 2007, 2009, 2010 (presented by coauthor), 2011 (invited, thematic session), 2012 (presented by coauthor), 2013 (roundtable), 2016

Annual conference of the British Sociological Association, 2011, 2013, 2018

Annual meeting of the Social Science History Association, 1999, 2000, 2003, 2004 (also organized panel), 2013, 2016

Sexual Identities Conference, London Society of the New Lacanian School, 2023

1968-2018: Fifty Years After, Scuola Normale Superiore, Florence, 2018

Generational Experience / Transformational Experience of 1968, European Solidarity Centre, Gdańsk, 2018

Cultural Transmission and Social Norms, University of East Anglia, 2017

Conference of the European Consortium for Sociological Research (keynote), 2016

Annual conference of the Political Studies Association, 2014

Conference of the Political Studies Association’s Methodology Group, 2017

Social Movements and Protest, University of Brighton, 2016

‘Alternative Futures and Social Protest’, Manchester Metropolitan University, 2001, 2014, 2016, 2017

Annual workshop on Analytical Sociology / Conference of the International Network of Analytical Sociologists, 2008, 2010, 2016

Annual conference of the Social History Society, 2009

Annual meeting of the Irish Conference of Historians, 2009

Annual conference of the Women's History Network, 2009

'Imprisonment and the Irish', Mater Dei Institute of Education, City University of Dublin, 2009

'Crossing Borders', Wissenschaftszentrum Berlin für Sozialforschung, 2006

'Power Laws in the Social Sciences', George Mason University, 2003

Invited seminars

Chinese University of Hong Kong, 2021

Charles University, Prague, 2018

Centre for Human and Social Sciences, Superior Council for Scientific Research, Madrid, 2018

Department of Social Sciences, Carlos III University, Madrid, 2018

Department of Sociology, University of Edinburgh, 2017

School of Sociology, University College Dublin, 2016

School of Social Sciences, Education and Social Work, Queen's University Belfast, 2016

'Interdisciplinary Perspectives on Modelling Conflict', University of Essex, 2016 (keynote)

Auro University, Surat, India, 2016

'Urban Insecurity and Civil Conflict', Nuffield College, Oxford, 2015

Institute for Analytical Sociology, Linköping University, 2015

Forum for Civil Society and Social Movement Research, University of Gothenburg, 2015

Department of Sociology, University of Cambridge, 2015

Department of History, Victoria University of Wellington, 2015

'The Power of the People: The Dynamics and Limits of Social Mobilization in South Eastern Europe', St Antony's College, Oxford, 2015 (keynote)

'Hunger Striking and Medical Ethics: Historical and Modern Perspectives', Centre for History of Medicine in Ireland, University of Ulster, 2015

'Political Engagement and Political Alternatives in the Age of Austerity in Europe', University of Birmingham, 2015

Contentious Politics Research Seminar, London School of Economics, 2013, 2015

Department of Sociology, University of Essex, 2013

'Suicide Protest: Normative Intrusions', Amherst College, 2013

Faculty of Sociology, Higher School of Economics Moscow, 2013

Summer School, University of Essex, 2012

'Tibet is Burning: Self-immolations, Ritual or Political Protest', Collège de France, 2012

Collegio Carlo Alberto, Turin, 2011

Centro Dondena, Università Bocconi, Milan, 2011

Institute for Social Change, University of Manchester, 2009

European Studies Center, University of Washington, 2009

Juan March Institute, Madrid, 2009

Social and Political Theory Group, Australian National University, 2008

Department of History, Victoria University of Wellington, 2008

Department of Sociology, University of Surrey, 2008

Department of Sociology, University of Kent at Canterbury, 2008

Complexity Seminar, Brunel University, 2007

ESRC Social Capital Seminar, University of Nottingham, 2006

Department of Political and Social Sciences, Universidad Pompeu Fabra, Barcelona, 2004

Department of Sociology, Illinois State University, 2004

Comparative Politics Workshop, University of Chicago, 2003

Other publications

'Research evidence: Gender-Atypical Tots Likely to Become Gay or Lesbian', 4thWaveNow, 7 August 2018

'The Open Society Foundations and the Transgender Movement', 4thWaveNow, 25 May 2018

Review of Emily Beaulieu's *Electoral Protest and Democracy in the Developing World,* in *Mobilization*, vol. 21, no. 1, 2016, pp. 137-8

(with Kenneth T. Andrews) 'Sit-ins and Desegregation in the U.S. South in the Early 1960s', ICPSR 35630, Inter-university Consortium for Political and Social Research, 2015

(with Neil Ketchley) 'Who Actually Died in Egypt's Rabaa Massacre', *Washington Post* Monkey Cage Blog, 14 August 2015

(with Neil Ketchley) 'What Is the Egyptian Anti-Coup Movement Protesting for?', *Washington Post* Monkey Cage Blog, 4 April 2014

Review of Matthew Lange's *Educations in Ethnic Violence: Identity, Educational Bubbles, and Resource Mobilization*, in *British Journal of Sociology*, vol. 64, no. 1, 2013, pp. 184-85

'Prophecy, Self-Fulfilling/Self-Defeating', *Encyclopedia of Philosophy and the Social Sciences*, ed. Byron Kaldis, Thousand Oaks, Calif.: Sage Publications, 2013, vol. 2, pp. 765-6

'Self-Immolation in Context, 1963-2012', *Revue d'Etudes Tibétaines*, no. 25, 2012, pp. 143-50

'Storm in a Teacup? A Comment on Ullmann-Margalit', *Norms and Values: The Role of Social Norms as Instruments of Value Realisation*, ed. Michael Baurmann, Geoffrey Brennan, Bob Goodin, and Nicholas Southwood, Baden-Baden: Nomos Verlagsgesellschaft, 2010, pp. 143-48

'Dying for a Cause—Alone?', *Contexts*, vol. 7, no. 2, 2008, pp. 22-27

Review of Matthias Reiss (ed.), *The Street as Stage: Protest Marches and Public Rallies since the Nineteenth Century*, in *Cultural and Social History*, vol. 6, no. 2, 2009, pp. 250-52

Review of Stathis N. Kalyvas, *The Logic of Violence in Civil War,* in *American Journal of Sociology*, vol. 113, no. 2, 2007, pp. 558-60

Review of Marek M. Kaminski, *Games Prisoners Play: The Tragicomic Worlds of Polish Prison*, in *American Journal of Sociology*, vol. 110, no. 6, 2005, pp. 1820-22

Review of Maryjane Osa, *Solidarity and Contention: Networks of Polish Opposition*, in *Social Forces*, vol. 83, no. 1, 2004, pp. 447-49

Review of Beverly J. Silver, *Forces of Labor: Workers' Movements and Globalization since 1870*, *Contemporary Sociology*, vol. 33, no. 4, 2004, pp. 467-69

'A Century of American Exceptionalism: Review Essay on Seymour Martin Lipset and Gary Marks, *It Didn't Happen Here: Why Socialism Failed in The United States*', *Thesis 11*, no. 68, 2002, pp. 110-21

Review of James C. Scott, *Seeing Like a State: How Certain Schemes to Improve the Human Condition Have Failed*, *Comparative Studies in Society and History*, vol. 44, no. 4, 2002, pp. 852-54

Review of Stephen K. Sanderson, *Social Transformations: A General Theory of Historical Development*, *Contemporary Sociology*, vol. 26, no. 1, 1997, pp. 47-48

Contributor to *New Zealand Historical Atlas*, ed. Malcolm McKinnon, Wellington: David Bateman in association with Historical Branch, Department of Internal Affairs, 1997

Kevin Hince, with Kerry Taylor, Jacqui Peace, and Michael Biggs, *Opening Hours: History of the Wellington Shop Employees Union*, Wellington: Wellington Shop Employees Union, 1990

Research grants

'Social Contexts of Islamist Activism in the United Kingdom', £2,483 awarded by the Economic and Social Research Council's Knowledge Exchange Dialogues Scheme, 2015

'Student Protest and Digital Media: The Campaign Against Tuition Fees', £6,914 awarded by the John Fell OUP Research Fund (102/671), 2011

'Protest Demonstrations in London over Two Centuries', £25,315 awarded by the John Fell OUP Research Fund (072/616), 2008-09

'Hunger Strikes by Suffragettes and Irish Republicans, 1909-1923: Compiling a Database of Individuals and Events', £71,873 awarded by the British Academy (LRG-45549), 2007-09

'Hunger Strikes Against British Rule, 1909-1933: Campaigns for Women's Suffrage, Irish Independence, and Indian Independence', $12,335 awarded by the University of Illinois Research Board, 2004-05

'Self-immolation: A Global Dataset, 1963-2002', £4,216, awarded by the Economic and Social Research Council (000-22-033), 2002

Media

Online and newswire: BBC World News online; BBC News magazine; Associated Press; France 24 online; France TV; Inter Press Service news agency; Al Jazeera; *Foreign Policy*; *Washington Post*'s Monkey Cage

Radio: Outlook and Newshour on BBC World Service; Today on BBC Radio 4; Archive Hour on BBC Radio 4; All Things Considered, Talk of the Nation, The Takeaway, and Interfaith Voices on National Public Radio; Public Radio International; Voice of America; CBC Radio; The Wide Angle on Newstalk Radio Ireland; Rear Vision, Australian Broadcasting Corporation; The Wire, Australia

Television: BBC Newsnight; BBC London TV

Newspaper: *Daily Telegraph*; *Sunday Times*; *Toronto Star*; *Times of India*

PROFESSIONAL SERVICE

Editorial Board of *Mobilization* (from 2007), *Social Forces* (from 2012), *Irish Journal of Sociology* (from 2018); consulting editor for *American Journal of Sociology* (2012-14)

Reviewer for *American Journal of Sociology* (35), *Social Forces* (29), *Mobilization* (19), *American Sociological Review* (16), *British Journal of Sociology* (9), *Social Movement Studies* (9), *European Sociological Review* (5), *Social Science History* (5), *Sociological Methods and Research* (4), *Sociological Forum* (4), *Social Problems* (3), *Comparative Political Studies* (3), *Social Science Research* (3), *International Review for the Sociology of Sport* (3), *Sociological Theory* (2), *World Politics* (2), *Political Studies* (2), *Journal of Peace Research* (2), *Journal of Comparative Politics* (2), *Theory and Society* (2), *Ethnic and Racial Studies* (2), *Acta Sociologica* (2), *Environmental Science and Policy* (2), *Politics, Religion and Ideology* (2), *Archives of Sexual Behavior* (2), *Journal of Early Adolescence* (2), *American Political Science Review*, *Proceedings of the National Academy of Sciences*, *British Journal of Political Science*, *Sociology*, *PLOS One*, *American Journal of Physics*, *Nature Climate Change*, *Organization Studies*, *Political Behavior*, *British Politics*, *Journal of Policy History*, *Qualitative Sociology*, *Urban Studies*, *Journal of Historical Sociology*, *International Labor and Working-Class History*, *Sociological Compass*, *Social Currents*, *Sexuality and Culture*, *American Journal of Physics*, *Journal of Political Philosophy*, *Research in Social Movements, Conflicts and Change*, *Poetics*, *Research and Politics*, *European Societies*, *Security Studies*, *Policy and Politics*, *Journal of Women, Politics and Policy*, *Journal of Controversial Ideas*, *Journal of Medical Ethics*, *Transcultural Psychology*, Oxford Bibliographies

Reviewer for ESRC First Grant Scheme; Volkswagen Stiftung; Netherlands Organisation for Scientific Research; Wellcome Trust, Medical History and Humanities Fellowship; Swiss National Science Foundation; Israel Science Foundation; Irish Research Council

Reviewer for Routledge (2), Polity, Sage's Quantitative Applications in the Social Sciences, Zed Books

External member of committee to appoint Associate Professor of Sociology, University of Konstanz, 2020

Organizer, Sessions on Collective Behavior, annual meeting of the American Sociological Association, 2005 and 2013

TEACHING

Completed doctoral students

Sandra Gonzalez-Bailon, 'Mapping Civil Society on the Web: Networks, Alliances and Informational Landscapes' (2007); Associate Professor of Communication, Annenberg School for Communication, University of Pennsylvania

Thomas Grund, 'Antecedents and Consequences of Social Networks: Macro-Implications of Micro-Dynamics' (2010, jointly with Peter Hedström); Professor of the Chair of Methods of Empirical Social Research, RWTH Aachen University

Christina Fuhr, 'The Construction and Perpetuation of Jewish Identity in Contemporary Britain' (2013, jointly with Gabriella Elgenius)

Samina Luthfa, 'Confronting the Juggernaut of Extraction: Local, National, and Transnational Mobilization against the Phulbari Coal Mine in Bangladesh' (2013); Associate Professor of Sociology, University of Dhaka

Rebeca Ibarra Olivares, 'Social Mechanisms of Tax Behaviour' (2013)

Raheel Dhattiwala, 'Hindu-Muslim Violence in Gujarat, 2002: Political Logic, Spatial Configuration, and Communal Cooperation' (2013)

Fei Yan, 'The Politics of Factional Conflict and Collective Violence: The Cultural Revolution in Guangzhou, 1966-1968' (2014); Associate Professor of Sociology, Tsinghua University

Juta Kawalerowicz, 'How Social Context Influences Political Participation in 21st-Century Britain, from Rioting to Voting' (2016); Postdoctoral Researcher, Department of Human Geography, Stockholm University, Sweden

Rima Majed, 'The Shifting Salience of Sectarianism in Lebanon, 2000-2010' (2016); Assistant Professor of Sociology, American University of Beirut

Effrosyni Charitopoulou, 'The European Refugee Crisis in Greece: Understanding Host Communities' (2020); Postdoctoral Researcher, Department of Politics and International Relations, University of Oxford

Christopher Barrie, 'Dynamics of Conflict and Revolution in Iraq and Tunisia' (2020); Lecturer in Computational Sociology, University of Edinburgh

Adam Brodie, 'Why Parades Are Peaceful: A Study of Mobilisation, Segregation, and Authority in Northern Ireland, 2006-2006' (2020, jointly with Dr Robin Harding)

Nicholas Martindale, 'The Impact of Outsourcing on State School Systems: The Case of the Academies Programme in England' (2021); Postdoctoral Prize Research Fellow, Nuffield College, Oxford

Arun Frey, 'Them Against Us: Assessing the Causes and Consequences of Anti-Immigrant Violence During the German Refugee Crisis', 2021; Postdoctoral Fellow, Leverhulme Centre for Demographic Science, Department of Sociology, University of Oxford

Courses designed and taught

Social Movements: Illinois, undergraduate; Oxford, graduate

Introduction to Social Statistics: Illinois and Queen's, undergraduate

Classical Sociological Theory: Illinois, graduate *(ranked excellent, fall 2004)*; Queen's, undergraduate

Analytical Sociological Theory: Oxford, graduate and undergraduate

Social Dynamics—Theories, Models, Methods: Illinois, graduate

Sociological Analysis: Oxford, graduate

Introduction to Sociology: Illinois, undergraduate

Explaining Knowledge: Harvard, undergraduate

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LETTER TO THE EDITOR

Puberty Blockers and Suicidality in Adolescents Suffering from Gender Dysphoria

Michael Biggs[1]

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According to Turban, King, Carswell, and Keuroghlian (2020), suicidal ideation is lower in transgender adults who as adolescents had been prescribed "puberty blockers"—gonadotropin-releasing hormone analogs (GnRHa). This finding was derived from a large nonrepresentative survey of transgender adults in the U.S., which included 89 respondents who reported taking puberty blockers. Turban et al. (2020) tested six measures of suicidality and three other measures of mental health and substance abuse. With multivariate analysis, only one of these nine measures yielded a statistically significant association: the respondents who reported taking puberty blockers were less likely to have thought about killing themselves than were the respondents who reported wanting blockers but not obtaining them. This finding was widely reported in the media; the lead author published a column on its implications for health policy in the *New York Times* (Turban, 2020).

Unfortunately, the finding came from a low-quality survey which is known to have elicited unreliable answers on puberty blockers. The analysis assumed that puberty blockers were available in the U.S. several years before they actually were. Most seriously, Turban et al. (2020) barely acknowledged the fact that adolescents with severe psychological problems would have been less eligible for drug treatment, which confounds the association between treatment and suicidal ideation. The article therefore provided no evidence to support the recommendation "for this treatment to be made available for transgender adolescents who want it" (Turban et al., 2020, p. 7).[1]

Turban et al. (2020) analyzed data from the United States Transgender Survey of 2015 (James et al., 2016). Respondents were not sampled from any defined population, but were recruited online. This convenience sample excluded those who underwent medical intervention and then subsequently stopped identifying as transgender. Obviously, those who actually committed suicide are omitted. Aside from these general problems with the survey, the key questions on puberty blockers evidently confused many respondents. Puberty blockers are given below the age of 16 years, when adolescents become eligible for cross-sex hormones (Hembree et al., 2009). Yet, 73% of respondents who reported having taken puberty blockers (question 12.9) said they started on them *after* the age of 18 years. As the survey report acknowledged, "the question may have been misinterpreted by some respondents who confused puberty blockers with the hormone therapy given to adults and older adolescents" (James et al., 2016, p. 126). Turban et al. (2020) did not mention this misinterpretation but did follow the report's mitigation strategy of ignoring those respondents who reported taking puberty blockers after the age of 18. No such adjustment is possible, however, for the question asking whether the respondent had ever wanted puberty blockers (question 12.8), which Turban et al. (2020) used to define the subset of respondents in their analysis. The comparison group therefore included an unknown number of respondents—possibly the majority—who actually wanted cross-sex hormones.

The subsample was confined to respondents who were aged under 18 in 1998, because Turban et al. (2020, p. 3) assumed that they "would have had health care access to GnRHa for pubertal suppression." GnRHa was first used to treat "juvenile transsexuals" in the Netherlands in the mid-1990s, with the first case study published in 1998 (Cohen-Kettenis & van Goozen, 1998; Gooren & Delemarre-van der Waal, 1996). But it took several years for the U.S. to follow suit. An early advocate was Spack, a pediatric endocrinologist at Boston Children's Hospital, who remembers "salivating" when he first heard about the Dutch model (Hartocollis, 2015). Although this hospital provided cross-sex hormones from 1998, puberty blockers were not offered until Spack co-founded its Gender Management

Editor's note. This Letter was peer reviewed by three members of the Editorial Board and myself.

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[1] The journal that published the target article, *Pediatrics*, rejected an earlier version of this Letter as an online comment without providing a reason.

Service in 2007 (Spack et al., 2012). That was the first specialized gender clinic for children in the U.S. (cf. Zucker, 2015). Only in 2009 did the Endocrine Society recommend puberty suppression for gender identity disorder (as gender dysphoria was then known); Spack helped to write its guidelines (Hembree et al., 2009). "There was an attitudinal shift to be able to say that the Endocrine Society supports this," he recalled a few years later (Ruttimann, 2013, p. 19). If one had to choose a year from which puberty blockers became generally available in the U.S., it would be 2009. This periodization is supported by complete data on prescriptions of one formulation of GnRHa (histrelin acetate) from 43 children's hospitals: it was never prescribed for gender identity disorder between 2004 and 2009 and was then prescribed to 92 patients from 2010 to 2016 (Lopez, Solomon, Boulware, & Christison-Lagay, 2018). That also accords with Turban and Keuroghlian's (2018, p. 451) own statement that transition for young (American) adolescents has been recommended "[d]uring the past 10 years." Faulty periodization means that Turban et al.'s (2020) subsample included older respondents who, in fact, had no opportunity to obtain these drugs and so cannot be used for comparison.

In discussing their results, Turban et al. (2020, p. 7) briefly admitted the possibility that "those without suicidal ideation had better mental health when seeking care and thus were more likely to be considered eligible for pubertal suppression." Indeed, the Endocrine Society's initial guidelines restricted eligibility to adolescents who "[d]o not suffer from psychiatric comorbidity that interferes with the diagnostic work-up or treatment" and "[h]ave adequate psychological and social support during treatment" (Hembree et al., 2009, p. 3138). The revised stipulation is that "[a]ny coexisting psychological, medical, or social problems that could interfere with treatment…have been addressed, such that the adolescent's situation and functioning are stable enough to start treatment" (Hembree et al., 2017, p. 3878). There is evidence that such guidelines are followed in clinical practice, at least to an extent. Gender Management Service at Boston Children's Hospital, for example, does not accept patients with severe psychopathology (Ruttimann, 2013). Analysis of 109 adolescents at one clinic demonstrates that patients who reported more psychological and social problems were less likely to receive puberty blockers, controlling for several other factors (Zucker et al., 2011).

Psychological problems are, therefore, a confounding factor that will create a spurious association between suicidality and treatment. The confounding could be resolved only if we could properly measure the respondent's psychological problems *before* GnRHa was prescribed or withheld.[2] Without any such measures, a negative association found many years after treatment is compatible with three scenarios: puberty blockers reduced suicidal ideation; puberty blockers had no effect on suicidal ideation; puberty blockers increased suicidal ideation, albeit not enough to counteract the initial negative effect of psychological problems on eligibility. Turban et al. (2020, p. 7) acknowledged that "the study's cross-sectional design… does not allow for determination of causation." Such caution was not conveyed in many news reports generated by the study. "Puberty blockers reduce suicidal thoughts in trans people" ran a typical headline (LGBTQ Nation, 2020).

In sum, then, Turban et al. (2020) contributed nothing to our knowledge of the effects of suppressing puberty in adolescents. One study did demonstrate positive psychological effects, based on measures taken from between 41 and 57 individuals, with no control group (de Vries, Steensma, Doreleijers, & Cohen-Kettenis, 2011). A second study cited by Turban et al. (2020) actually showed no statistical difference in improvement in psychological functioning between the group prescribed puberty blockers and the group given therapy (Biggs, 2019; Costa et al., 2015). "Longitudinal clinical trials are needed to better understand the efficacy of pubertal suppression," as Turban et al. (2020, p. 7) observed. It is remarkable that such a call is necessary nearly a quarter of a century after this treatment was first proposed.

[2] Parental support and social class are additional confounding factors, though the analysis did control for these—albeit poorly, as the variables pertain to the respondent's current situation and not their situation before treatment.

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Letter to the Editor

Michael Biggs*

Revisiting the effect of GnRH analogue treatment on bone mineral density in young adolescents with gender dysphoria

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To the Editors,

I write to respond to Joseph, Ting, and Butler's recent article, describing the effect of administering gonadotropin-releasing hormone analogue (GnRHa) to suppress puberty in adolescents diagnosed with gender dysphoria [1]. The mean of the patients' bone mineral density (BMD)—relative to the norm for their sex and age—declined significantly over 2 years. What really matters is the lower tail of the distribution, but this information was omitted by Joseph et al. This letter analyses individual data on 24 patients from Joseph et al.'s sample of 31 [2]. It finds that after 2 years of GnRHa, up to a third of patients had abnormally low bone density, in the lowest 2.3% of the distribution for their sex and age. A few patients recorded extremely low values, in the lowest 0.13% of the distribution. This finding undermines Joseph et al.'s conclusions.

The Dutch pioneers of this experimental treatment for gender dysphoria warned that patients could 'end with a decreased bone density, which is associated with a high risk of osteoporosis' [3]. The effects on bone density have been described by four Dutch studies [4–7], besides Joseph et al. BMD is measured by a dual energy X-ray absorptiometry (DXA) scan over the spine (lumbar) and the hip (femoral neck). The absolute value of BMD is standardized as a Z-score, expressing this individual's BMD relative to the population of the same sex and age. BMD can be adjusted for height to derive the volumetric bone mineral apparent density (BMAD), which is likewise standardized as a Z-score.

A Z-score below −2 is considered low; it indicates bone density in the lowest 2.3% of the population of the same sex and age [8]. Joseph et al. argue that 'this is not the sole definition of low bone mass in children, nor is this criterion a recognized predictor of later fracture risk'. But this threshold was prominent in the experiment which introduced puberty suppression for gender dysphoria to Britain. The original experimental protocol (co-authored by Butler) in 2010 excluded any child with a spine or hip BMD Z-score below −2. In 2012, however, this exclusion criterion was relaxed 'in exceptional circumstances'—if clinicians 'feel that on the balance of risks, pubertal suppression is an appropriate option despite risks of osteoporosis in later adult life' and patients 'understand the risks of GnRH analogue treatment for bone density (i.e., risks of later osteoporosis)' [9].

Information on the lower tail of the distribution of Z-scores—below −2—is omitted by Joseph et al. and by three out of four Dutch studies. Describing distributions by mean (and standard deviation) is not sufficient when clinical concern focuses on very low values. This will be illustrated for patients experiencing 2 years of puberty suppression. Joseph et al.'s sample after 24 months on GnRHa comprised 31 patients. Data on 24 of these patients —or at least patients from the same clinic at University College London Hospital—have recently been released, though sex is unavailable [2]. These patients were enrolled in the British experiment which recruited patients from 2011 to 2015. The Stata do file to replicate the analysis is posted at https://doi.org/10.7910/DVN/FSOMME.

Table 1 shows mean Z-scores for Joseph et al.'s three measures of BMD, at baseline and at 24 months (the hip measure is missing for three patients). The 2011–15 sample is naturally similar to Joseph et al.'s. The decline in the mean of all three scores is statistically significant in both samples ($p \leq 0.004$ in every paired t-test).

Using data from the 2011–15 sample, Figure 1 depicts the distributions of Z-scores at 24 months, along with the

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Table 1: Bone density in adolescents undergoing puberty suppression.

	Hip BMD		Spine BMD		Spine BMAD	
	Joseph et al.	2011–15	Joseph et al.	2011–15	Joseph et al.	2011–15
Mean Z-score at baseline	−0.58	−0.55	−0.44	−0.34	−0.09	−0.46
Mean Z-score at 24 months	−1.40	−1.45	−1.64	−1.46	−0.71	−1.28
Change in Z-score	−0.82	−0.90	−1.20	−1.12	−0.62	−0.81
p-value (two-tailed)	0.000	0.000	0.000	0.000	0.000	0.004
n	31	21	31	24	31	24

BMD, bone mineral density; BMAD, bone mineral apparent density.

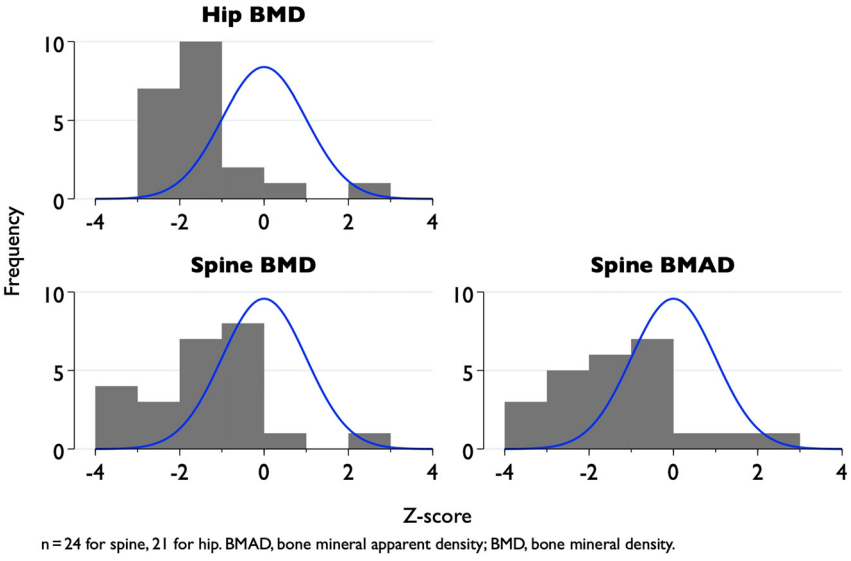

Figure 1: Bone density after 24 months of puberty suppression.

Normal distribution to compare with the population of the same sex and age. For hip BMD, a third of patients had a low Z-score, below −2. For spine BMD, more than a quarter of patients had low Z-scores. The lower tail extended far beyond. Indeed, four patients had Z-scores below −3, putting them in the bottom 0.13% of the population. Adjusting for height, by computing spine BMAD, does not shrink the lower tail.

Given that puberty suppression left up to a third of patients with abnormally low bone density, Joseph et al.'s recommendations are surprisingly complacent. One is to reduce DXA monitoring which 'can have significant financial implications for healthcare providers'. Another is to change the computation of Z-scores; 'reference ranges may need to be re-defined for this select patient cohort'. Rather than altering a measure that provides inconvenient findings, practitioners of puberty suppression must record fractures as adverse events. One British patient who started GnRHa at age 12 then experienced four broken bones by the age of 16 [10]. This history, if it were combined with BMD Z-scores below −2, would meet the diagnostic criteria for paediatric osteoporosis [11]. Whether this case is exceptional is unknown because clinicians have failed to collect relevant data.

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LETTER TO THE EDITOR

Suicide by Clinic-Referred Transgender Adolescents in the United Kingdom

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Introduction

Surveys show that adolescents who identify as transgender are vulnerable to suicidal thoughts and self-harming behaviors (dickey & Budge, 2020; Hatchel et al., 2021; Mann et al., 2019). Little is known about death by suicide. This Letter presents data from the Gender Identity Development Service (GIDS), the publicly funded clinic for children and adolescents aged under 18 from England, Wales, and Northern Ireland. From 2010 to 2020, four patients were known or suspected to have died by suicide, out of about 15,000 patients (including those on the waiting list). To calculate the annual suicide rate, the total number of years spent by patients under the clinic's care is estimated at about 30,000. This yields an annual suicide rate of 13 per 100,000 (95% confidence interval: 4–34). Compared to the United Kingdom population of similar age and sexual composition, the suicide rate for patients at the GIDS was 5.5 times higher. The proportion of patients dying by suicide was far lower than in the only pediatric gender clinic which has published data, in Belgium (Van Cauwenberg et al., 2021).

Suicidality in Transgender Adolescents

"About half of young trans people…attempt suicide," declared the United Kingdom Parliament's Women and Equalities Committee (2015). Similar figures are cited by news media and campaigning organizations. The *Guardian* reported Stonewall's statistic that "almost half" of transgender young people "have attempted to kill themselves" (Weale, 2017). "Fifty percent of transgender youth attempt suicide before they are at age 21" stated the mother of the most famous transgender youth in the English-speaking world (Jennings & Jennings, 2016). As a transgender theologian has observed, "the statistic about suicide attempts has, in essence, developed a life of its own" (Tanis, 2016).

Representative surveys of students in high schools provide one source of evidence for this statistic. In New Zealand, 20% of transgender students reported attempting suicide in the past 12 months, compared to 4% of all students (Clark et al., 2014). In the United States, 15% of transgender students reported a suicide attempt requiring medical treatment in the last 12 months, compared to 3% of all students (Centers for Disease Control & Prevention, 2018; Jackman et al., 2021; Johns et al., 2019). In another American survey, 41% of transgender students reported having attempted suicide during their lifetime, compared to 14% of all students (Toomey et al., 2018).

To what extent are self-reported suicide attempts reflected in fatalities? The connection is not straightforward. Respondents who report suicide attempts are not necessarily indicating an intent to die. One survey of the American population found that almost half the respondents who reported attempting suicide subsequently stated that their action was a cry for help and not intended to be fatal (Nock & Kessler, 2006). In two small samples of non-heterosexual youth, half the respondents who initially reported attempting suicide subsequently clarified that they went no further than imagining or planning it; for the remainder who did actually attempt suicide, their actions were usually not life-threatening. To an extent, then, "the reports were attempts to communicate the hardships of lives or to identify with a gay community" (Savin-Williams, 2001). Although such elaborate survey methods have not been used to study transgender populations, there is anecdotal evidence for a similar disjuncture. The pediatric endocrinologist who established the first clinic for transgender children in the United States stated that "the majority of self-harmful actions that I see in my clinic are not real suicide attempts and are not usually life threatening" (Spack, 2009).

Suicide mortality has been studied in the transgender population using registry data. The annual suicide rate is calculated by dividing the number of suicides by the total number of years each person was at risk. An individual who was observed for 20 years, for instance, contributes 20 person-years to the denominator. The

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largest study covers over 8,000 patients who visited the gender clinic in Amsterdam from 1972 to 2017 (Wiepjes et al., 2020). The annual suicide rate was 29 per 100,000 for transmen, quadruple the rate for the female population, and 64 for transwomen, quadruple the rate for the male population. A Swedish study of 324 individuals who had undergone genital surgery between 1973 and 2003 found much higher annual suicide rates: 250 per 100,000 for transmen, 43 times the rate for matched female controls, and 285 for transwomen, 16 times the rate for matched male controls (M. Boman, personal communication, 12 April 2021; Dhejne et al., 2011). Only one published study has reported suicide fatalities among transgender adolescents. Belgium's pediatric gender clinic provided counseling to 177 youth aged from 12 to 18 years, who had been referred between 2007 and 2016: five of them (2.8%) committed suicide (Van Cauwenberg et al., 2021). The mean age of referral was 15, implying a mean duration of 3 years before transition to an adult clinic, which translates to an annual suicide rate of 942 per 100,000. This is the highest suicide mortality recorded for any transgender population.

Method

This Letter estimates the suicide rate at the world's largest pediatric gender clinic. Based in London, the GIDS is part of the Tavistock and Portman NHS Foundation Trust, and serves youth under 18 from England, Wales, and Northern Ireland who are "experiencing difficulties with their gender identity development" (Carmichael & Davidson, 2009). Like all such services throughout Western Europe and North America, it has experienced enormous growth; referrals increased from 100 in 2009 to a peak of 2700 in 2019. The waiting list in April 2021 exceeded 5300.

The GIDS patients manifest typically high rates of self-harming behavior. In a sample of 900 adolescents (aged from 13 to 17) admitted to the clinic from 2009 to 2017 and given the Youth Self-Report questionnaire, 44% answered that they sometimes or very often "deliberately try to hurt or kill myself" (de Graaf et al., 2020). Unfortunately, both behaviors are combined in this question. In a different sample of over 700 children and adolescents (aged from 4 to 17) assessed by the GIDS in 2012 and 2015, 10% were flagged by clinicians as having attempted suicide (Morandini et al., 2021).

Suicides

Since the early 2000s, the National Health Service has implemented mandatory reporting of "serious incidents" (Department of Health, 2001, 2010). The death of any patient—including those on the waiting list—suspected to be suicide is reported to the Tavistock's Board of Directors. The Tavistock cooperates with a comprehensive surveillance system for every death classified as suicide or (after an open verdict by the coroner) probable suicide in the United Kingdom (National Confidential Inquiry into Suicide & Homicide by People with Mental Illness, 1999; National Confidential Inquiry into Suicide and Safety in Mental Health, 2019). Papers for the Tavistock's Board meetings are available from April 2007 onwards; those not on the Trust's website were acquired by a Freedom of Information request. The pdf files of the *Agenda and Papers* (through September 2021) were searched for the keyword "suicid"; all 442 instances were inspected. From 2007 to 2020, four patients of the GIDS died by suspected suicide: two on the waiting list, in 2016 and 2017; and two after having been seen, in 2017 and 2020. The last case was described as "likely" to be suicide, because the inquest has not yet been held. These figures were confirmed by Freedom of Information requests to the Tavistock.

Triangulation is possible from two sources. Comprehensive mortality data on all adolescents aged from 10 to 19 who committed suicide in the United Kingdom from 2014 to 2016 include five transgender individuals (Rodway et al., 2020). Due to confidentiality restrictions, it is not possible to disaggregate these further by age or by country. Presumably, one of these is the patient of GIDS who died in 2016. The remaining four might have been 18 or 19—the risk of suicide increases significantly in the late teens—or might have lived in Scotland. Alternatively, they might have been eligible for the GIDS but had not sought a clinical referral (made by the local Child and Adolescent Mental Health Service, the child's general practitioner, social worker, or teacher) or had not obtained it.

Another source is the Transgender Day of Remembrance website, which aims to record all deaths by suicide or violence (Metcalfe, 2021). For the United Kingdom between 2007 and 2020, the website names 3 adolescents under the age of 18 who committed suicide. One was one of the GIDS patients (the match is certain because they were named in the *Agenda and Papers*). The other two had no involvement with the GIDS (or any other gender clinician), as was evident from their inquests, though one was under the psychiatric care of another NHS Trust (BBC News, 2021; Bunyan, 2008). In addition, the website lists suicides by two "young" transgender people, sourced from Twitter, without information on their name or age. In one case, it is not clear whether the person lived in the United Kingdom.

Patients

With suicides as numerator, two denominators are relevant. Because comprehensive data on patient numbers became available from 2010, the period will be the 11 years from 2010 to 2020. (These are financial years; thus, 2020 runs from April 2020 to March 2021.) The first denominator is the total number of individual patients, estimated by summing the annual number of referrals to the GIDS from 2010 to 2020—excluding those aged 18 or over, as they are not accepted. The total number is 15,032. This sum omits patients at the clinic who had been referred before

2010, and so is a slight underestimate. (The Online Supplement provides full details.)

The second denominator is the total number of patient-years: the sum of the number of years spent by each individual as a patient of the GIDS. The number of patients seen by the GIDS each year was available from 2014 to 2020. Before 2014 only the number of patients first seen was available. From 2014 to 2016, the number of patients seen was consistently double the number first seen, and so the former number for 2010 to 2013 was estimated by doubling the latter. All these numbers exclude patients on the waiting list. The number waiting at the beginning of each year from 2016 to 2020 was obtained by Freedom of Information request. Before then the number was not available, and so must be treated as zero. This leads to an underestimate, of course, but the waiting list became appreciable only from 2015. The total number of patient-years over this period is estimated as 30,080. In other words, patients spent on average 2 years at the GIDS (including time on the waiting list). Time on the waiting list contributed 41% of the total patient-years.

Results

From 2010 to 2020, the four suicide deaths equate to 0.03% of the 15,032 patients. Taking the denominator as 30,080 patient-years, the annual suicide rate is calculated as 13 per 100,000 (95% confidence interval: 4 to 34 per 100,000). For comparison, the annual suicide rate in England and Wales between 2010 and 2020 for adolescents aged from 15 to 19 years averaged 4.7 (Office for National Statistics, 2021). This does not quite correspond to the age range of the GIDS patients, however. At referral, the patients ranged in age from 3 to 17 years; only 7% were younger than 10. The mean was 14 years and the median 15. Most patients stay with the GIDS until transitioning to an adult service. Therefore, the average age of patients at any point in time will lie somewhere between 14 and 17. A better comparison is therefore the overall suicide rate for adolescents aged from 14 to 17 (available only for the entire United Kingdom for 2015–2017), which was 2.7 per 100,000 (Office for National Statistics, 2018; Rodway et al., 2020). Comparison should also account for the difference between the sexes, because males are more likely to commit suicide than females. Of the GIDS patients, 69% were female. Adjusting for sex, the GIDS patients were 5.5 times more likely to commit suicide than the overall population of adolescents aged 14 to 17.

Discussion

How reliable are these estimates? The chief uncertainty about the numerator is whether the fourth death will be ruled as suicide when the inquest is eventually held. It could be speculated that there were further suicides unknown to the Tavistock and to the National Confidential Inquiry into Suicide and Safety in Mental Health. All that can be said is that the single suicide by a GIDS patient from 2014 to 2016 is not out of line with comprehensive mortality data on suicides by transgender adolescents in the United Kingdom which counted five suicides in a longer age range and wider geographical area. The denominator for the annual suicide rate, however, is pieced together from various series and so is inevitably approximate. Statistics from the early 2010s are less reliable, though they make only a small contribution to the grand total; the last three years contribute more than half of the total number of patient-years. The most significant limitation is the lack of information on the age and sex of all the patients who committed suicide.

Direct comparison can be made with the Belgian pediatric gender clinic (Van Cauwenberg et al., 2021). Its annual suicide rate was about 70 times greater than the rate at the GIDS. This is especially puzzling because patients at the Belgian clinic scored better, on average, than those at the GIDS on tests of psychological functioning (de Graaf et al., 2018). The explanation for the huge disparity in suicide is not clear. The Amsterdam's clinic annual suicide rate was four times greater than the rate at the GIDS. The higher rate is not surprising, however, because the Dutch clinical population was dominated by older adults: the median age at first visit was 25 (Wiepjes et al., 2020). Suicide rates peak in middle age, and so a population of older adults would be at higher risk than a population of adolescents.

The suicide rate of the GIDS patients is not necessarily indicative of the rate among all adolescents who identify as transgender. On the one hand, individuals with more serious problems (and their families) would be particularly motivated to seek referral and more likely to obtain it, and so the clinical subset would be more prone to suicide. One study suggests that a child who frequently attempted suicide was more readily referred to the GIDS (Carlile et al., 2021). On the other hand, young people facing hostility from their families would be less able to seek referral, and this hostility could make them especially vulnerable to suicide.

Taking into account these limitations, the estimated suicide rate at the GIDS provides the strongest evidence yet published that transgender adolescents are more likely to commit suicide than the overall adolescent population. The higher risk could have various causes: gender dysphoria, accompanying psychological conditions, and ensuing social disadvantages such as bullying. Studies of young people referred to the GIDS in 2012 and 2015 found a high prevalence of eating disorders, depression, and autism spectrum conditions (ASC) (Holt et al., 2016; Morandini et al., 2021)—all known to increase the probability of suicide (Simon & VonKorff, 1998; Smith et al., 2018). Eating disorders and depression could be consequences of transgender identity and its ensuing social repercussions, but this is implausible for ASC insofar as it originates in genes or the prenatal environment. From a sample of over 700 referrals to the GIDS in 2012 and 2015, 14–15% were diagnosed with ASC (Morandini

et al., 2021). This compared to 0.8–1.1% of students in England (Department for Education, 2012, 2015). The association between autism and gender dysphoria is found in many populations (Socialstyrelsen, 2020; Warrier et al., 2020). Autism is known to increase the risk of suicide mortality, especially in females (Hirvikoski et al., 2016; Kirby et al., 2019; Socialstyrelsen, 2020). To some extent, therefore, the elevated suicide rate for transgender youth compared to their peers reflects the higher incidence of ASC. The same holds for other psychiatric disorders associated with gender dysphoria (Dhejne et al., 2016). Ideally, the suicide rate for patients of the GIDS would be compared to the suicide rate for patients in contact with other NHS mental health services, but the latter rate is not available.

One final caveat is that these data shed no light on the question of whether counseling or endocrinological interventions—gonadotropin-releasing hormone agonist or cross-sex hormones—affect the risk of suicide (Biggs, 2020; Turban et al., 2020). Although two out of the four suicides were of patients on the waiting list, and thus would not have obtained treatment, this is not disproportionate: the waiting list contributed nearly half of the total patient-years.

Conclusion

Data from the world's largest clinic for transgender youth over 11 years yield an estimated annual suicide rate of 13 per 100,000. This rate was 5.5 times greater than the overall suicide rate of adolescents of similar age, adjusting for sex composition. The estimate demonstrates the elevated risk of suicide among adolescents who identify as transgender, albeit without adjusting for accompanying psychological conditions such as autism. The proportion of individual patients who died by suicide was 0.03%, which is orders of magnitude smaller than the proportion of transgender adolescents who report attempting suicide when surveyed. The fact that deaths were so rare should provide some reassurance to transgender youth and their families, though of course this does not detract from the distress caused by self-harming behaviors that are non-fatal. It is irresponsible to exaggerate the prevalence of suicide. Aside from anything else, this trope might exacerbate the vulnerability of transgender adolescents. As the former lead psychologist at the Tavistock has warned, "when inaccurate data and alarmist opinion are conveyed very authoritatively to families we have to wonder what the impact would be on children's understanding of the kind of person they are…and their likely fate" (Wren, 2015).

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10508-022-02287-7.

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Declarations

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The Dutch Protocol for Juvenile Transsexuals: Origins and Evidence

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ABSTRACT

It has been a quarter of a century since Dutch clinicians proposed puberty suppression as an intervention for "juvenile transsexuals," which became the international standard for treating gender dysphoria. This paper reviews the history of this intervention and scrutinizes the evidence adduced to support it. The intervention was justified by claims that it was reversible and that it was a tool for diagnosis, but these claims are increasingly implausible. The main evidence for the Dutch protocol came from a longitudinal study of 70 adolescents who had been subjected to puberty suppression followed by cross-sex hormones and surgery. Their outcomes shortly after surgery appeared positive, except for the one patient who died, but these findings rested on a small number of observations and incommensurable measures of gender dysphoria. A replication study conducted in Britain found no improvement. While some effects of puberty suppression have been carefully studied, such as on bone density, others have been ignored, like on sexual functioning.

The use of Gonadotropin-Releasing Hormone agonist (GnRHa) drugs to suppress puberty in "juvenile transsexuals" was first proposed in print in the mid-1990s (Gooren & Delemarre-van de Waal, 1996). Developed by three clinicians at Utrecht and Amsterdam, this intervention became known as the Dutch protocol. It rapidly became standard practice in the treatment of adolescents diagnosed with gender dysphoria (HBIGDA, 2001). This intervention has been described in several manifestos by its proponents (e.g. de Vries & Cohen-Kettenis, 2012; Delemarre-van de Waal, 2014; Delemarre-van de Waal & Cohen-Kettenis, 2006) and subjected to brief critical commentaries (Byng et al., 2018; Laidlaw et al., 2019; Levine et al., 2022). The aim of this paper to provide an historical account of the invention of the Dutch protocol and a critical review of the evidence that has accumulated in the quarter of a century since it was proposed.

Before proceeding, some definitions are in order. Gender dysphoria will be used here to describe a persistent desire to become the opposite sex (Zucker, 2010). Medical terminology has changed over time, from "gender identity disorder" and "transsexualism" (both introduced in the *Diagnostic and Statistical Manual of Mental Disorders–III* in 1980) to "gender dysphoria" (as renamed in the 2013 *DSM–5*) and "gender incongruence" (as renamed in the 2019 *International Classification of Diseases–11*). There is no need to dwell on these diagnostic criteria because the condition in practice is defined by the patient's wish for endocrinological and surgical interventions. In the nomenclature of transgender medicine, "puberty blockers" denote GnRHa drugs (alternatively known as Luteinizing Hormone-Releasing Hormone agonists) which stop the production of sex hormones.[1] Drugs in this class include triptorelin (branded Decapeptyl or

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Gonapeptyl), which is used in the Netherlands and Britain, and leuprorelin (branded Lupron) in North America. GnRHa drugs are licensed to treat several medical conditions including precocious puberty in children; endometriosis and uterine fibroids in women; and advanced prostate cancer and sexual deviance in men. The drugs have never been licensed as a treatment for gender dysphoria.

The paper begins by describing how puberty suppression was invented, primarily by the psychologist Peggy Cohen-Kettenis, in the 1990s. It reveals the gap between the protocol described in formal manifestos and actual clinical practice. The second section examines the rationale for this intervention, focusing on two claims—that GnRHa is reversible and that it serves as diagnosis—and two omissions—the association between gender dysphoria and homosexuality and the effect of GnRHa on sexual development. The third section traces the international adoption of the Dutch protocol. The fourth section scrutinizes evidence from an early cohort of 70 adolescents subjected to puberty suppression at the Amsterdam clinic (de Vries et al., 2011, 2014). This cohort provides the only significant evidence that GnRHa followed by cross-sex hormones and surgery results in improved psychological function and reduced gender dysphoria. The evidence is less persuasive than it appears: the number of observations was considerably fewer than 70, the reported reduction in gender dysphoria depended on incommensurable scales, and the outcomes omit one patient who died because puberty suppression dictated a riskier vaginoplasty. The fifth section pursues the British study designed to replicate the Dutch one; it was withheld from publication for some years, presumably because puberty suppression in this sample failed to improve gender dysphoria or psychological functioning. The poor quality of American studies is also noted. The final section evaluates evidence for the side effects of GnRHa. The negative effect on the accrual of bone mass is well studied, while there is increasing evidence for negative effects on cognitive and emotional development and on sexual functioning.

Origins of the Dutch protocol

Transsexualism as a concept emerged in the mid-twentieth century, following the discovery of cross-sex hormones and advances in plastic surgery (Hausman, 1995). Novel physical interventions were justified by the new theoretical construct of "gender identity" invented by American psychologists and psychiatrists, most notably John Money (1994). Gender identity was conceived as developing in infancy (e.g. Green, 1968), but physical interventions for transsexuals under the age of 18 were vanishingly rare. Money in 1973 advised a doctor to prescribe testosterone to a 15-year-old girl and even to consider mastectomy—but he was unusually reckless and there is no evidence that his advice was followed (Gill-Peterson, 2018, pp. 163–164). Specialist clinics for children and adolescents with gender identity problems were founded in Toronto in 1975, in Utrecht in 1987, and in London in 1989. They provided counseling. Cross-sex hormones had to wait until the patient was referred to an adult clinic, at an age ranging from 16 to 18 (Bradley & Zucker, 1990). Surgeries were not performed under the age of 18 (Petersen & Dickey, 1995). Referrals of children were rare. The London clinic—the only specialized clinic for children with gender dysphoria in the United Kingdom—over its first decade accepted an annual average of 14 patients (Di Ceglie, 2018). In its first seven years the Utrecht clinic averaged 9 per year (Cohen-Kettenis, 1994).

Lowering the age of intervention was driven by the founder of the Utrecht children's clinic, Peggy Cohen-Kettenis. She had established herself in the field of gender medicine in the 1980s, presenting research to international conferences of the Harry Benjamin International Gender Dysphoria Association (HBIGDA), which had been formed by clinicians and academics. She eventually became professor of psychology in the Department of Child and Adolescent Psychiatry at University Medical Center Utrecht (Everaerd et al., 2014). She was closely connected to clinicians at VU Medical Center Amsterdam (affiliated with Vrije Universiteit Amsterdam), which housed the country's clinic for adult transsexuals.

Cohen-Kettenis believed that transsexuals would experience better outcomes if they started treatment before adulthood. By the mid-1990s, she was referring some patients aged 16 and 17 to the Amsterdam clinic for endocrinological intervention prior to cross-sex hormones (Cohen-Kettenis, 1994). Males were given an antiandrogen, cyproterone acetate, which prevented erections and caused breast tissue to grow; females were given progestin to stop menstruation (Gooren & Delemarre-van de Waal, 1996). Johanna, for example, "fulfilled all necessary requirements for early treatment": she did not favor girly things (though neither did her sisters), she was fond of soccer, she never dated in school (perhaps not surprising given that she was homosexual), and her parents discovered her wearing a tight t-shirt to conceal her breasts (Cohen-Kettenis et al., 1998, p. 124). Brought to the clinic at 17, she was prescribed progestin for four months and then testosterone. Within two years Jaap (as Johanna had become) underwent mastectomy, hysterectomy, and oophorectomy, and obtained a new birth certificate. Evidence to support such early treatment came from the first 22 patients from the Utrecht clinic, interviewed in their twenties, from one to five years after surgery (Cohen-Kettenis & van Goozen, 1997; Kuiper & Cohen-Kettenis, 1988). They were compared to a larger group of transsexuals who had transitioned later in adulthood in previous decades (Kuiper and Cohen-Kettenis 1988). Her former patients showed better psychological functioning and "more easily pass in the desired gender role" (Cohen-Kettenis & van Goozen, 1997, p. 270). One problem with the comparison is that they had transitioned in a more tolerant era. Another is the fact that they were still young; most had no sexual partner. Moreover they had not reached an age at which they might regret their inability to conceive children. (This group has not since been followed up.) Cohen-Kettenis' initiative was praised by Money: he singled out her contribution to a conference in London as "the bravest" (1998, p. xviii).

Cohen-Kettenis had two collaborators at Amsterdam. One was Henriette Delemarre-van de Waal, a pediatric endocrinologist. She had expertise using the new GnRHa drugs—developed in the 1980s—to treat precocious puberty and other conditions (e.g. Schroor et al. 1995). The other was Louis Gooren, ~~a psychiatrist~~ an~~d~~ endocrinologist who was installed as the world's first professor of transsexuality in 1989. His inaugural professorial lecture was addressed by Cohen-Kettenis and by Money, who flew over from Johns Hopkins University (Nederlands Tijdschrift voor Geneeskunde 1989). Like the pioneering generation who created transsexualism, Gooren saw gender dysphoria as an intersex condition: "there is a contradiction between the genetic, gonadal and genital sex on the one hand, and the brain sex on the other" and therefore "we must provide them with reassignment treatment which meets their needs" (Gooren, 1993, p. 238). This hypothesis was apparently vindicated when he coauthored an article in *Nature* showing that the volume of the central subdivision of the bed nucleus of the stria terminalis in six male-to-female transsexuals was closer to the volume found in females than in males (Zhou et al., 1995). "Unfortunately," as he recently acknowledged, "the research has never been replicated" (Gooren, 2021, p. 50; see also Kreukels & Burke, 2020).

GnRHa was introduced as a treatment for gender dysphoria in two articles. Gooren and Delemarre-van de Waal (1996) proposed the "Feasibility of Endocrine Interventions in Juvenile Transsexuals." More influential was a case study of the first "adolescent transsexual" treated with GnRHa (Cohen-Kettenis and van Goozen 1998). From the age of 5, FG "had made it very clear that I was supposed to be a boy" (FG, 2021, p. 131). It later transpired that FG was sexually attracted to women. FG's father, an Italian with traditional views on gender, disapproved of his daughter's masculinity, and serious conflict ensued. Extensive psychotherapy did not improve matters; FG wrote a suicide note at the age of 12. When FG was 13, Delemarre-van de Waal prescribed triptorelin.[2] Three years later, around 1990, FG came to the Utrecht gender clinic, and Cohen-Kettenis was impressed by FG's "boyish appearance" (Cohen-Kettenis, 2021, p. 115). The clinic provided therapy and introduced FG to other adolescent girls who identified as transsexual. (Whether FG was introduced to any adolescents who identified as lesbian is not recorded.) FG's puberty suppression continued until the age of 18, when testosterone commenced, followed by multiple surgeries: mastectomy, hysterectomy, oophorectomy, and

metaidoioplasty. Awaiting the last surgery at the age of 20, FG was "happy with his life" and "never felt any regrets"; gender dysphoria was apparently cured (Cohen-Kettenis & van Goozen, 1998, p. 247).

Puberty suppression remained exceptional for some years. By 2000, GnRHa had been administered to only 7 children under the age of 16 (Cohen-Kettenis et al., 2000). The new treatment regime was codified at VU Medical Center in Amsterdam, where Cohen-Kettenis was appointed professor of medical psychology in 2002, moving with her clinic. The "Dutch protocol" was published in an influential article in 2006, supported financially by Ferring Pharmaceuticals, the manufacturer of triptorelin (Delemarre-van de Waal & Cohen-Kettenis, 2006, p. S137). GnRHa could be administered to transsexuals as young as Tanner stage 2—marked by the first growth of pubic hair and for girls by budding breasts and for boys by growing testicles—as long as they had reached the age of 12. The adolescent would usually then begin "to live permanently in the role of their desired sex" (Delemarre-van de Waal & Cohen-Kettenis, 2006, p. S132). After some years of puberty suppression, the youth would start cross-sex hormones at the age of 16 and then surgeries at the age of 18. Eligibility criteria for puberty suppression appeared strict. First, gender dysphoria should have begun early in childhood, and dysphoria should have worsened with the onset of puberty. Second, the patient should be psychologically stable, and not suffer from other mental health problems. Third, the patient should have support from their family. As the protocol was formalized, the number of children undergoing puberty suppression increased markedly. Between 2000 and 2008, GnRHa was prescribed to 111 children, about one per month (de Vries et al., 2011). One of them was Valentijn de Hingh, the subject of a television documentary (Nietsch, 2007). After a teacher was disconcerted by the boy's passion for dolls, de Hingh at the age of 5 was diagnosed with gender dysphoria by Cohen-Kettenis (de Hingh, 2021). GnRHa was administered from the age of 12 in 2002.

The protocol as published was not always strictly followed by the clinicians. The minimum age of 12 for puberty suppression was not observed in every case (de Vries, 2010, p. 104). De Hingh had regular endocrinological checkups from the age of 10, presumably so that puberty suppression could commence as soon as Tanner stage 2 was reached. Likewise, cross-sex hormones sometimes started before the age of 16, as young as 13.9 years (de Vries et al., 2011, p. 2278). Family support was not essential, as the clinic administered GnRHa to a 14-year-old—who was institutionalized due to a physical handicap—against the parents' objections (Cohen-Kettenis and Pfäfflin 2003). A British television documentary from the mid-1990s provides a glimpse of actual practice (Morse, 1996). *The Wrong Body* took three English young people to Amsterdam and Utrecht, to see transgender medicine at its most advanced. Fredd Foley, aged 13, met Gooren to learn about puberty suppression; this was around the time it was proposed in the medical literature (Gooren and Delemarre-van de Waal 1996). After returning to England and being refused GnRHa by the London clinic, Foley's mother telephoned Gooren who agreed to write a three-month prescription of triptorelin. "If your child knows for sure he is transsexual," he said, "I would not let puberty happen." Gooren's willingness to prescribe drugs for a child in another country, met briefly in front of the cameras, against the wishes of the child's own psychiatrist, hints that the assessment process was not always as rigorous as portrayed in the published literature. As Cohen-Kettenis said in the documentary, "it's very difficult to give exact criteria, in some cases you have the feeling that the adolescent has thought about it and knows pretty well what she or he is doing."

The Dutch protocol scrutinized

The Dutch protocol comprised not just a drug (GnRHa) and a treatment regime (from age 12 or Tanner stage 2) but also two discursive claims. The first was reversibility. The initial article declared GnRHa to be "fully reversible; in other words, no lasting undesired effects are to be expected" (Gooren & Delemarre-van de Waal, 1996, p. 72). The phrasing hinted at the lack of actual evidence. Suppressing puberty for a short time, on the order of months, might be expected

to have a negligible effect on a child's development. Yet the Dutch protocol entailed suppression for up to four years (from age 12 to 16); for FG it lasted at least five years (from 13 to 18). It was implausible to claim that suppressing puberty for so many years would have no lasting effect if the child were to stop GnRHa and restart their natal sex hormones. On occasion this was acknowledged, as when Delemarre-van de Waal and Cohen-Kettenis' (2006, p. S137) manifesto stated that "It is not clear yet how pubertal suppression will influence brain development." Ten years later, however, Cohen-Kettenis still claimed that puberty suppression was "completely reversible" (Cohen-Kettenis, 2016; see also de Vries et al., 2016). The postulate of reversibility, however implausible, helped to avoid the question of whether a child aged 12 (or below) could give consent to this endocrinological experiment. HBIGDA's Standards of Care warned that cross-sex hormones "are not, or are not readily, reversible" (HBIGDA, 1985, p. 83). By pronouncing GnRHa to be reversible, the Dutch protocol demarcated a boundary between one endocrinological intervention and another.

The second claim was that puberty suppression was a diagnostic tool. The case study of FG described GnRHa as an "aid in diagnosis and treatment" (Cohen-Kettenis & van Goozen, 1998). This echoed the conception of cross-sex hormones as "both therapeutic and diagnostic in that the patient requesting such therapy either reports satisfaction or dissatisfaction regarding the results" (HBIGDA, 1985, p. 85). GnRHa was posited to provide space for therapeutic exploration of gender identity, without the pressure of the physical changes accompanying puberty (Delemarre-van de Waal & Cohen-Kettenis, 2006). This claim was plausible, though it was also plausible that stopping normal cognitive, emotional, and sexual development would impede such exploration. In the event, the Dutch clinicians found that the diagnostic test invariably yielded the same result: "none of the [54] patients who were selected for pubertal suppression has decided to stop taking GnRHa" (Delemarre-van de Waal & Cohen-Kettenis, 2006, p. S136). This might be explained by a rigorous selection process. An alternative explanation is that puberty suppression becomes a self-fulfilling prophecy. Subsequent experience in the Netherlands and in other countries confirms the fact that 96%–98% of children who undergo puberty suppression continue to cross-sex hormones (Brik et al., 2020; Carmichael et al., 2021; Wiepjes et al., 2018).

The framing of GnRHa as diagnostic circumvented a problem recognized in the earliest articles. "Not all children with GID [Gender Identity Disorder] will turn out to be transsexuals after puberty," acknowledged Cohen-Kettenis and Gooren (1999, p. 319). "Prospective studies of GID boys show that this phenomenon is more closely related to later homosexuality than to later transsexualism." They cited three longitudinal studies of feminine boys (Green, 1987; Money & Russo, 1979; Zuger, 1984).[3] The best known is Richard Green's attempt at "studying pretranssexuals" by selecting a group of "sissy boys" (Green, 1987, p. 12). After fifteen years, to his surprise, only one out of 44 was contemplating transsexuality, whereas two thirds had become bisexual or homosexual men. Given such studies, Cohen-Kettenis concluded that "most GID children under 12 will not grow up to become transsexuals" (Cohen-Kettenis & van Goozen, 1997, p. 246). These findings were downplayed in subsequent publications; the key manifestos for the Dutch protocol did not mention homosexuality and did not cite any study of feminine boys (Cohen-Kettenis et al., 2008; Delemarre-van de Waal & Cohen-Kettenis, 2006). The assertion that "GID persisting into early puberty appears to be highly persistent" rested on slender evidence (Cohen-Kettenis et al., 2008, p. 1895). The only relevant cited source described adolescents who had been first assessed at ages ranging from 13 to 18, a range extending well beyond early puberty (Smith et al., 2001). This source did not support the hypothesis that the probability of gender dysphoria persisting to adulthood jumped suddenly on the cusp of age 12, from under 50% to virtually 100%. What is known is that most adolescents subjected to puberty suppression were homosexual. Of the first 70 adolescents referred to the Amsterdam clinic from 2000 to 2008 and given GnRHa, 62 were homosexual while only 1 was heterosexual (de Vries et al., 2011).

The crucial advantage of puberty suppression was creating "individuals who more easily pass in to the opposite gender role" (Delemarre-van de Waal & Cohen-Kettenis, 2006, p. 155). The emphasis was on external appearance, especially height.[4] That word appears 23 times in

Delemarre-van de Waal's review of puberty suppression (Delemarre-van de Waal, 2014). There is one cursory reference to "loss of fertility." The words orgasm, libido, and sexuality do not appear. This is curious because it was well known that men taking GnRHa for prostate cancer experience complete loss of erotic interest (Marumo et al., 1999). The drug is therefore licensed to chemically castrate men with sexual obsessions. Gooren was an early advocate for this usage. He warned that the side effects "may be very uncomfortable" for men with paraphilias (Gijs & Gooren, 1996, p. 279); no such warning accompanied his recommendation of the same drug for adolescents experiencing gender dysphoria. The Dutch clinicians did not ask whether blocking the normal development of erotic desire would affect their patients' understanding of their own body and their interest in future sexual and romantic relationships.

One significant disadvantage of puberty suppression for males was not mentioned in the 2006 manifesto for the Dutch protocol, though it had been raised at a conference in the previous year (GIRES, 2005). Stopping sexual development meant the penis did not grow, and so "the genital tissue available for vaginoplasty may be less than optimal" (Cohen-Kettenis et al., 2008, p. 1895). This made it more likely that the orifice would need to be lined with a portion of the patient's intestine rather than the inverted penis (van de Grift et al., 2020). Out of 49 patients at Amsterdam who started GnRHa at Tanner stage 2 or 3, 71% required intestinal vaginoplasty (van der Sluis et al., 2021). This procedure is more invasive, requiring a second surgical site, and it entails greater risk of complications such as rectal fistula. Surgical techniques have been refined so that the "possible occurrence of intestinal discharge could be kept under control" (Bouman, 2021, p. 141), but one quarter of the patients need further corrective surgeries (Bouman et al., 2016).

International adoption of the Dutch protocol

The Dutch protocol immediately attracted interest in other countries. Cohen-Kettenis and Gooren were already prominent in the field of transgender medicine, exemplified by their election to the Board of Directors of HBIGDA (the former served two four-year terms from 1995 and 2003, while the latter served one term from 1999). Puberty suppression soon entered HBIGDA's Standards of Care in the Sixth Version, approved in 2001. It closely followed the Dutch protocol, but did not specify any minimum age. It was "recommended that the adolescent experience the onset of puberty in his or her biologic sex, at least to Tanner stage Two," while also allowing earlier intervention on the recommendation of more than one psychiatrist (HBIGDA, 2001, p. 10). Recall that the published evidence for the benefits of puberty suppression then comprised a single case study of one patient—FG—awaiting final surgery.

In the United States, adoption was led by Norman Spack, a pediatric endocrinologist. More than once he recalled "salivating" at the prospect of treating patients with GnRHa (Hartocollis 2015; Spack 2008, xi). In 2007 he cofounded the Gender Management Service at Boston Children's Hospital, which was the first dedicated clinic for transgender children in America. Its program was based on the Dutch model; the hospital sent a psychologist to Amsterdam to be trained by Cohen-Kettenis (Tishelman et al., 2015). From the outset the Boston clinic offered GnRHa at Tanner stage 2 or 3 with no minimum age (Spack et al. 2012). Spack joined Cohen-Kettenis, Gooren, and Delemarre-van de Waal on the Endocrine Society's committee tasked with writing their first clinical guidelines for "transsexual persons," which recommended GnRHa for children at Tanner stage 2 or 3 (Hembree et al., 2009). "There was an attitudinal shift to be able to say that the Endocrine Society supports this," he later recalled (Ruttimann, 2013, p. 19). The shift is visible in data from 43 children's hospitals on prescriptions of one GnRHa drug (histrelin acetate): it was never prescribed for gender dysphoria between 2004 and 2009 and was then prescribed to 92 patients from 2010 to 2016, most in the final years of the period (Lopez et al., 2018).

Oprah Winfrey Television broadcast the documentary *I Am Jazz: A Family in Transition* in 2011 (Stocks, 2011). Its dramatic structure was similar to *The Wrong Body*, focusing on the

looming threat of puberty as Jazz Jennings reached the age of 11. Jennings had been diagnosed with gender dysphoria at the age of 3 and had appeared on national television at the age of 7, when the family created the TransKids Purple Rainbow Foundation (Jennings & Jennings, 2016). The documentary showed the family consulting with a pediatric endocrinologist, who confirmed that Tanner stage 2 had been reached. The denouement was not shown, but Jenning's mother was clear: "you have to kinda nip puberty in the bud, you want to block it" (Stocks, 2011). Jennings did indeed commence puberty suppression some months later. The number of clinics for "gender-nonconforming children and adolescents" multiplied, and within a few years 32 of them advertised puberty blockers (Hsieh & Leininger, 2014).

England provides an example of adoption driven by patients rather than clinicians. *The Wrong Body* had promoted the Dutch approach to 3 million viewers (Nataf, 1999). Dissatisfaction at the cautious policy of the London clinic—still headed by its founder, Domenico Di Ceglie—became increasingly vocal. Sustained pressure came from the parents of children who identified as transgender, organized in the Gender Identity Research and Education Society (GIRES) and Mermaids. GIRES obtained funding from medical charities to organize an international symposium in London in 2005 to develop consensus guidelines for endocrinological intervention, which was attended by Cohen-Kettenis, Delemarre-van de Waal, and Spack. GIRES (2006) warned that "those who can in any way afford to do so have to consider taking their children to the USA." The first was Susie Green, later the chief executive of Mermaids. In 2007 she took her son Jackie, aged 12, to Boston to obtain GnRHa from Spack (Sloan, 2011). A presentation at Mermaids instructed parents in this medical tourism (Mermaids, 2007). Spack treated seven more British children over the next few years (Glass, 2012). The conflict between parents and clinicians climaxed in 2008, with two clashing conferences. The Royal Society of Medicine organized a meeting on adolescent gender dysphoria, which drew criticism for the lack of overseas speakers advocating for puberty blockers, even though it had invited Delemarre-van de Waal. The cofounder of GIRES, whose child had transitioned in their late teens two decades earlier, used the new epithet "transphobic" to describe the cautious clinicians (Groskop, 2008). Richard Green—the author of *Sissy Boys*, then in London as a visiting professor—quickly organized a rival conference to demand puberty suppression (Green, 2008). Speakers included the usual cast of clinicians, including Spack, and also patients and their parents, including two Dutch transgender adolescents. The demand for puberty suppression was becoming irresistible.

Di Ceglie was soon replaced as director of the London clinic (renamed the Gender Identity Development Service and located at the Tavistock and Portman NHS Foundation Trust) by Polly Carmichael, a clinical psychologist. The clinic in 2011 began to offer GnRHa from the age of 12, initially as part of an experimental study (Biggs, 2019b, 2019c). Before any outcomes were published, Carmichael declared success: "Now we've done the study and the results thus far have been positive we've decided to continue with it" (Manning and Adams, 2014). She even appeared on BBC Children's Television to promote puberty suppression, in a documentary about a 13-year-old girl who wanted to be a boy, Leo. Carmichael reassured Leo about GnRHa: "the good thing about it is, if you stop the injections, it's like pressing a start button and the body just carries on developing as it would if you hadn't taken the injection" (Niland, 2014). In 2015 the National Health Service adopted a policy of offering GnRHa for adolescents at Tanner stage 2, without age restriction (NHS England, 2015).

Evidence from the Amsterdam clinic

By the mid-2010s, then, the Dutch protocol was established as the standard for transgender medicine. It was apparently vindicated when longitudinal data was published on a cohort of 70 adolescents referred to the clinic between 2000 and 2008 and then subjected to puberty suppression. The lead author, Annelou de Vries, received her doctorate under the supervision of Cohen-Kettenis. Outcomes were initially measured as the patient was transitioning from GnRHa to cross-sex hormones, at ages ranging from 14 to 19. "Behavioral and emotional problems and

depressive symptoms decreased, while general functioning improved" (de Vries et al., 2011, p. 2276). Outcomes were subsequently measured soon after the patient's final surgery (vaginoplasty or mastectomy and hysterectomy with oophorectomy), at ages ranging from 19 to 22. The authors concluded that "gender dysphoria had resolved, psychological functioning had steadily improved, and well-being was comparable to same-age peers" (de Vries et al., 2014, p. 696).

When scrutinized, however, the evidence is less persuasive. The sample was small: final outcome measures were available for subsets of patients numbering between 32 and 55. The finding that gender dysphoria had resolved depended on the Utrecht Gender Dysphoria Scale and the Body Image Scale, which have separate questionnaires for each sex. The researchers switched versions over the course of the study (Levine et al., 2022). A boy who wanted to become a girl, for example, answered the male questionnaires at baseline before puberty suppression, and then the female versions following surgery—so would be rating agreement with the statement "I hate menstruating because it makes me feel like a girl" (C. Schneider et al., 2016) and satisfaction with "ovaries-uterus" (Lindgren & Pauly, 1975). The inclusion of such meaningless questions compromises the measurement of change in gender dysphoria. The results after surgery exclude eight patients who refused to participate in the follow-up or were ineligible for surgery, and one patient killed by necrotizing fasciitis during vaginoplasty. The authors did not mention the fact that this death was a consequence of puberty suppression: the patient's penis, prevented from developing normally, was too small for the regular vaginoplasty and so surgery was attempted with a portion of the intestine, which became infected (Negenborn et al., 2017). A fatality rate exceeding 1% would surely halt any other experimental treatment on healthy teenagers.

One inevitable limitation of the study was the measurement of results soon after surgery, which repeated the problem with the first study of adolescent transsexuals (Cohen-Kettenis & van Goozen, 1997). As Cohen-Kettenis notes, "a truly proper follow-up needs to span a minimum period of 20 years" (Cohen-Kettenis, 2021, pp. 117–118). A subsequent follow-up of this cohort is in preparation (Bazelon, 2022). The only long-term outcome published in the literature is that of the very first patient, FG, who was followed up again at the age of 35. FG did not regret transition, but scored high on the measure for depression. Owing to "shame about his genital appearance and his feelings of inadequacy in sexual matters," he could not sustain a romantic relationship with a girlfriend (Cohen-Kettenis et al., 2011, p. 845). Ironically, a "strong dislike of one's sexual anatomy" is one of the diagnostic criteria for gender dysphoria in children (according to *DSM*-5), and so in this respect it is not clear how the dysphoria had been resolved. The clinicians were more interested in FG's height, which they compared punctiliously to the Italian as well as the Dutch height distribution. Cohen-Kettenis concluded that "the negative side effects are limited" (Cohen-Kettenis et al., 2011, p. 843). Delemarre-van de Waal's (2014, p. 194) summary was even more optimistic: "He was functioning well psychologically, intellectually, and socially." Now aged 48, FG has given two recent interviews. FG's situation seems to have improved, and he now has a serious girlfriend. He describes puberty suppression as "life-saving" in his case (FG, 2021, p. 132) but also recommends that it should require a significant assessment process (Bazelon, 2022). In a recent interview, Valentijn de Hingh, who at the age of 31 now identifies as non-binary, emphasizes that "diagnosis and treatment at a young age were not wrong." At the same time, de Hingh wonders "wasn't that very young? To have been seeing a psychologist, having been examined and diagnosed from the age of five" (de Hingh, 2021, p. 182).

Replicating the Dutch results

An international study of puberty suppression—involving London and Boston as well as Amsterdam—was first mooted in 2005 (GIRES, 2005). The Boston clinic dropped out, but eventually an experiment along Dutch lines was begun in London in 2010. The entry criteria were "consistent with the protocol used at the Amsterdam Gender Clinic" (Viner et al., 2010, p. 6) and the outcome measures replicated those used by the Amsterdam longitudinal study (de

Vries et al., 2011, 2014). From 2011 to 2014, 44 adolescents aged from 12 to 15 years commenced puberty suppression. Outcomes for all subjects after two years on GnRHa were thus collected by 2016. Preliminary results were presented to the World Professional Association for Transgender Health (as HBIGDA had been renamed) in Amsterdam. In her keynote address, Carmichael observed that "our results have been different to the Dutch" (Carmichael, 2016). According to one presentation, adolescents after one year of GnRHa "report an increase in internalising problems and body dissatisfaction, especially natal girls" (Carmichael et al., 2016). Another presentation was also negative: "Expectations of improvement in functioning and relief of the dysphoria are not as extensive as anticipated, and psychometric indices do not always improve nor does the prevalence of measures of disturbance such as deliberate self harm improve" (Butler, 2016). These conference papers were not published as articles, following the typical fate of medical experiments that fail to produce positive results (Johnson & Dickersin, 2007).

Instead, the London clinic published an article claiming that "adolescents receiving also puberty suppression had significantly better psychosocial functioning after 12 months of GnRHa … compared with when they had received only psychological support" (Costa et al., 2015, p. 2206). The group subjected to puberty suppression were aged between 13 and 17, and must have included some of the 44 experimental subjects. This group comprised 101 adolescents at the outset, diminishing to 35 after twelve months. This high rate of attrition was not explained in the article. Anyway, the data showed no statistically significant difference between the group given GnRHa and counseling and the group given only counseling (Biggs, 2019a).

The full outcomes from the experiment were published following a protracted campaign involving publicity in newspapers and television (e.g. Tominey & Walsh, 2019), complaints to the ethics committee which approved the research (Health Research Authority, 2019), a Parliamentary question (Blackwood of North Oxford, 2019), and a judicial review (Keira Bell and Mrs A v Tavistock NHS Trust, 2020). Out of the 44 subjects in the experiment, all but one transitioned to cross-sex hormones. Outcomes were taken after 12 months of puberty suppression for all patients, and after 24 months for the subset waiting to reach the age of 16 when they could start cross-sex hormones. The headline finding was that "GnRHa treatment brought no measurable benefit nor harm to psychological function in these young people," and gender dysphoria likewise did not improve (Carmichael et al., 2021, p. 20). This is all the more surprising because a placebo response would be expected in patients who had volunteered to pioneer this intervention in Britain (Kirsch, 2019). There was no disaggregation by sex, which is unfortunate because outcomes were evidently worse for natal girls than for boys (Biggs, 2020; Carmichael et al., 2016).

The researchers did not compare their findings to the outcomes from the Amsterdam clinic after puberty suppression (de Vries et al., 2011). Comparison is undertaken here, using available data on two question batteries.[5] The Youth Self-Report (YSR) enables the adolescent to describe their problems, while the Child Behavior Checklist (CBCL) provides a parent's assessment. YSR and CBCL each yield three *T*-scores: one for Internalizing Problems like anxiety; one for Externalizing Problems like anger; and a Total Problem score, combining these two along with other problems such as social isolation (Achenbach & Rescorla, 2001). *T*-scores are normalized relative to reference scores (for males and for females aged 12–18), with a mean of 50 and standard deviation of 10. The Amsterdam clinic reported these measures for 54 subjects, compared to 41 for the London clinic. The two samples were similar at the outset of puberty suppression: the mean age at Amsterdam was 14.8, the median at London was 13.6; females comprised 53% of the Amsterdam sample, 43% of the London one. Figure 1 depicts the mean scores at baseline before the commencement of puberty suppression, along with the 95% confidence interval. There was no discernible difference between the Amsterdam and London samples in any component of CBCL or YSR. At the Amsterdam clinic, the subjects completed the questionnaires again when they transitioned to cross-sex hormones, after a mean of 1.9 years. At the London clinic, the questionnaires were completed at 12-month intervals, and so I take the latest available before the end of puberty suppression; the mean duration is 1.4 years. Figure 2

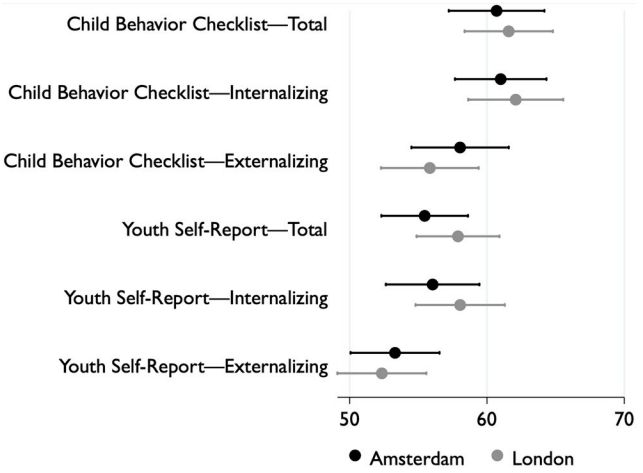

Figure 1. Psychological functioning before puberty suppression with GnRHa. The circle shows the mean *T*-score at baseline. The line traces the 95% confidence interval. $N = 54$ at Amsterdam, 41 at London. Data from de Vries et al. (2011, Table 2) and Carmichael et al. (2021).

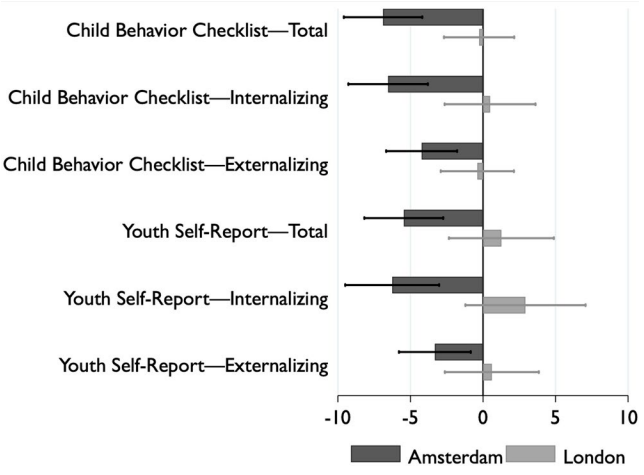

Figure 2. Change in psychological functioning after puberty suppression with GnRHa. The bar shows the change in *T*-score from baseline; negative values indicate reduced problems. The line traces the 95% confidence interval. $N = 54$ at Amsterdam, 41 at London. Data reported from de Vries et al. (2011, Table 2) and Carmichael et al. (2021).

shows how the scores changed since baseline. The Amsterdam sample improved—fewer problems were reported by the subjects and their parents—on all six measures (p = .000004 … .003). The London sample, by contrast, experienced no discernible change (p = .16 … .82). With one exception (YSR Externalizing Problems), the differences between the change in Amsterdam and the change in London are statistically significant (p = .0006 … .03, assuming equal variance).

The London clinic's failure to replicate the positive results found by the Amsterdam clinic after puberty suppression demonstrates that the Dutch results cannot be extrapolated to other countries. The reason for the failure to replicate could perhaps lie in the quality of care offered by the clinics or in the characteristics of their patients. Although the two samples had indistinguishable baseline scores on YSR and CBCL, on another measure of psychological functioning—the Children's Global Assessment Scale (CGAS), which is scored by the clinician—the adolescents attending the London clinic were significantly worse at the outset. This fits the general pattern in adolescents referred to European gender clinics: those at Amsterdam have fewer psychological problems and better peer relationships than those at London (de Graaf et al., 2018). The failure

to replicate could simply exemplify a general phenomenon in medicine (and science generally): a large effect found in a nonrandomized study with a small sample usually either declines in magnitude or disappears altogether in subsequent studies (e.g. Ioannidis, 2005). Given the London clinic's failure to find favorable results after puberty suppression, it has no incentive to follow up the 43 subjects who transitioned to cross-sex hormones and potential surgery. It loses track of all its patients after the age of 18, blaming "the frequent change in nominal and legal identity, including NHS number in those referred on to adult services" (Butler et al., 2018, p. 635).

One other clinic has published a comparable longitudinal study of puberty suppression. The Hamburg Gender Identity Service followed 11 adolescents who were administered GnRHa for an average of one year, but such a tiny sample provides insufficient statistical power for any conclusions (Becker-Hebly et al., 2021). Three American studies of puberty suppression have been published: from Stony Brook (Achille et al., 2020), Dallas (Kuper et al., 2020), and Seattle (Tordoff et al., 2022).[6] None tried to replicate the Amsterdam and London longitudinal studies, choosing completely different measures, with one exception (BIS is used by Kuper et al., 2020). Each introduced a different set of measures: Quick Inventory of Depressive Symptoms, Screen for Child Anxiety Related Emotional Disorders, Center for Epidemiologic Studies Depression Scale, Quality of Life Enjoyment and Satisfaction Questionnaire, Generalized Anxiety Disorder 7-item scale, and the Patient Health Questionnaire 9-item scale. The last scale was common to two studies, but even they were not comparable: one used the version for teenagers, the other the adult version which the researchers chose to dichotomize. All the samples were tiny: 19, 23 (including an unspecified number of males given anti-androgens and females given medroxyprogesterone rather than GnRHa), and 25. Results were reported inconsistently: sometimes the outcomes for the sample subjected to puberty suppression were combined with a much larger sample on cross-sex hormones; sometimes the parameters of complex multivariate models were reported while the within-subject change during puberty suppression was concealed (Singal, 2022). Finally, some results were vitiated by high—and unexplained—rates of attrition: 47% of the subjects in one study were excluded because they failed to fill in the questionnaires at three points in time (Achille et al., 2020). What is frustrating is that if these researchers had simply followed the methods of de Vries et al. (2011), these three small samples would have contributed to cumulative knowledge. Finally, a large-scale American study recruited 90 subjects for puberty suppression—from Boston, Chicago, Los Angeles, and San Francisco—between 2016 and 2018 (Olson-Kennedy et al., 2019). Outcomes after 24 months have evidently been collected, but only baseline results have been published (Chen et al., 2021).

Evidence on side effects

On the side effects of puberty suppression, there is most evidence on bone density. That GnRHa would cause "an insufficient formation of bone mass" was initially dismissed "of no great concern" (Gooren & Delemarre-van de Waal, 1996, p. 72). Then it was recognized that patients could "end with a decreased bone density, which is associated with a high risk of osteoporosis" (Delemarre-van de Waal & Cohen-Kettenis, 2006, p. S134). The detrimental effect of GnRHa on the accrual of normal bone mass has been documented in several longitudinal studies from the Amsterdam clinic (Klink et al., 2015; Schagen et al., 2020; Stoffers et al., 2019; Vlot et al., 2017), the London clinic (Biggs, 2021; Joseph et al., 2019), and a clinic in Ottawa (Navabi et al., 2021). Less obviously, adolescents who seek GnRHa for gender dysphoria have a lower distribution of bone density compared to the population of the same sex and age (see also Lee et al., 2020). This reflects in part the high prevalence of eating disorders.

Bone mineral density (BMD) is measured by a dual energy X-ray absorptiometry scan over the spine and the hip. The absolute value of BMD is standardized as a *Z*-score, expressing this individual's BMD relative to the population of the same sex and age. BMD can be adjusted for height to derive the volumetric bone mineral apparent density (BMAD), which is likewise standardized as a *Z*-score. A *Z*-score below −2 is considered low; it indicates bone density in the

lowest 2.3% of the population. The salience of this threshold is revealed by the London clinic's protocol which required both spine and hip *Z*-scores to exceed −2 to be eligible for GnRHa (Viner et al., 2010). This was subsequently relaxed "in exceptional circumstances" if clinicians "feel that on the balance of risks, pubertal suppression is an appropriate option despite risks of osteoporosis in later adult life" and patients "understand the risks of GnRH analogue treatment for bone density (i.e. risks of later osteoporosis)" (Viner et al., 2012).

Most studies of bone density after puberty suppression summarize the distribution of *Z*-scores by mean and standard deviation; only two provide information on the lower tail of the distribution, which is what matters clinically. At the Amsterdam clinic, 56 transgender adolescents were treated with GnRHa, commencing at ages ranging from 11 to 18, for an average duration of 1.7 years. After puberty suppression, the minimum *Z*-score for spine BMAD was −2.4, and the minimum hip BMAD was −3.4 (Vlot et al., 2017). Normally we would expect to find a *Z*-score below −3 in only 0.13% of the population—1 in 741. At the London clinic, 24 adolescents were treated with GnRHa, commencing at ages ranging from 12 to 14, for a duration of 24 months. After puberty suppression, the hip BMD *Z*-score was below −2 for 7 patients. The spine BMD *Z*-score was below −2 for 7 patients, including 4 patients with *Z*-score below −3; the spine BMAD *Z*-score was below −2 for 8 patients, including 3 with *Z*-score below −3 (Biggs, 2021). Clearly, then, a significant minority of patients have abnormally low bone density after puberty suppression. The subsequent administration of cross-sex hormones increases bone mass, but *Z*-scores remain below the baseline recorded at the outset of puberty suppression (Klink et al., 2015; Stoffers et al., 2019; Vlot et al., 2017), with the possible exception of females who take testosterone after starting GnRHa early in puberty (Schagen et al., 2020).

What is not clear is the consequence of abnormally low bone density. Information on fractures, for example, has been published only for adults taking cross-sex hormones who had not undergone puberty suppression (Wiepjes et al., 2020). Anecdotally, a female patient at the London clinic who started GnRHa at age 12 then experienced four broken bones by the age of 16 (Bannerman, 2019). A Swedish television documentary discovered one female who was given GnRHa from age 11 to 15 by the Karolinska University Hospital in Stockholm, and now suffers from severe osteoporosis, including continual skeletal pain (SVT, 2022). This case—along with two others whose puberty suppression was terminated following concerns about bone density—led Sweden to restrict the use of GnRHa for adolescents with gender dysphoria.

The effects of puberty suppression on emotional and cognitive development are more difficult to ascertain, but more consequential as they could potentially affect the capacity to consent to cross-sex hormones and surgery. One case report of puberty suppression commencing just before age of 12 measured a drop in IQ by 10 points after 28 months (M. A. Schneider et al., 2017). A single case is insubstantial, of course, but there are similar findings from children treated with GnRHa for precocious puberty. A study of 25 children measured a drop of 7 points after two years (Mul et al., 2007); another study found a gap of 8 points between 15 treated children and a matched control group (Hayes, 2017; Wojniusz et al., 2016). Unfortunately the Amsterdam clinic's longitudinal study of puberty suppression measured IQ only at baseline and did not measure it again (de Vries et al., 2011, 2014). A small study from the clinic found that 8 adolescent males undergoing puberty suppression performed worse in a test of executive functioning than three control groups; the differences are statistically significant, but the samples are small (Staphorsius et al., 2015). Randomized control trials of non-human animals provide evidence of the substantial effects of puberty suppression. In sheep, GnRHa impairs spatial memory, and this effect remains after the treatment is stopped—thus demonstrating the irreversibility of puberty suppression (Hough et al. 2017a; 2017b). Counterintuitively, GnRHa also leads to greater differences between males and females in foraging behavior (Wojniusz et al., 2011). In mice, the effects of GnRHa vary by sex: males develop stronger preference for other males and an increased stress response; females exhibit increased anxiety and despair-like behavior (Anacker et al., 2021).

Even less is known about the effects of puberty suppression on sexual functioning. Jennings, who started on GnRHa at the age of 11, has no libido and cannot orgasm. Jennings' surgeon,

Marci Bowers, who has performed over 2,000 vaginoplasties, acknowledges that "every single child … who was truly blocked at Tanner stage 2, has never experienced orgasm. I mean, it's really about zero" (Bowers, 2022). This remark refers to males. The effects of puberty suppression at such an early stage on females is unknown. FG is reportedly able to orgasm (de Vries et al., 2011). One patient at the London clinic who took GnRHa from the age of 12 to 16 but did not continue to cross-sex hormones has experienced no sexual desire in the two years since ceasing GnRHa (Bannerman, 2022). According to de Vries, orgasm is "a very interesting and so far not studied question" (Klotz, 2022).

Conclusion

The use of GnRHa to suppress puberty has proved more popular than could have been envisaged in the mid-1990s. It has become the international standard for treating gender dysphoria and has attracted increasing numbers of patients. Down to 2015, the Amsterdam clinic administered GnRHa to a total of 333 youth aged under the age of 18 (Wiepjes et al., 2018). From 2012 to 2020, the London clinic administered GnRHa to 344 children under the age of 15. Both clinics were overwhelmed by referrals from the mid-2010s, and the lengthening waiting lists provided scope for unscrupulous commercial operations. GenderGP, for example, is a company registered in Singapore and owned by a Welsh doctor which will diagnose a 9-year-old with gender dysphoria over video and prescribe GnRHa on the same day (Medical Practitioners Tribunal Service, 2022). The total number of patients subjected to puberty suppression, worldwide, must run to several thousand. The proponents of GnRHa never reassessed the rationale for the intervention as the numbers multiplied. It is one thing to assert that very rare cases of extreme gender dysphoria—one per year in the Netherlands in the late 1990s—should be treated as juvenile transsexuals. It is another to make this claim for numerous adolescents—currently over a hundred a year in the Netherlands. Given the fact that gender dysphoria lacks an objective diagnosis, the potential for puberty suppression is expansive. When a recent survey in one American school district found 7% of students identifying as "gender diverse," the authors urged that all receive "access to gender affirming care," which in effect means giving GnRHa on request (Kidd et al., 2021, p. 3).[7]

Whether the availability of puberty suppression has increased demand is a question that should be raised. Taking GnRHa early in puberty promises a more passable resemblance to the opposite sex, and this is why it proved so fascinating to television audiences. It is no coincidence that media coverage of transgender youth focuses on those who suppressed puberty at a young age, most famously Jennings. Positive media coverage is known to increase referrals to gender clinics, at least over the short term (Indremo et al., 2022; Pang, de Graaf, et al., 2020). Although Dutch clinicians advise against "a complete social transition … before the very early stages of puberty" (de Vries & Cohen-Kettenis, 2012, pp. 308–309), the availability of GnRHa now makes it feasible for parents to treat a young child as the opposite sex, which guarantees that the child will experience the onset of puberty as catastrophic and thus demand endocrinological intervention. For boys, social transition prior to puberty is a powerful predictor of gender dysphoria persisting into adolescence, even controlling for the degree of dysphoria in childhood (Steensma et al., 2013). This pathway is illustrated by interviews with 30 British parents who had started raising their children as the opposite sex between the ages of 3 and 10. According to one parent, "If you don't give a child puberty-blockers there is a consequence—it's not that nothing happens. There's a massive consequence" (Horton, 2022, p. 13). Another candidly described their child's attitude to counseling at the gender clinic: "at the end of the day, he's just gonna say whatever it is, that makes you shut up, so that he can get the blocker" (Horton, 2022, p. 14).

What has happened to the majority of children with gender dysphoria who used to grow up into gay or lesbian adults? The original articles promoting GnRHa (Cohen-Kettenis & van Goozen, 1998; Gooren & Delemarre-van de Waal, 1996) hypothesized that children whose dysphoria persisted to the age of 12 were destined to become transsexual. This arbitrary age threshold

was soon forgotten. Outside the Netherlands, GnRHa was adopted with no minimum age, and has been prescribed to children as young as 8 years old.[8] Delemarre-van de Waal eventually advocated for GnRHa to be administered before Tanner stage 2, "right at the onset of puberty," followed quickly by cross-sex hormones (Delemarre-van de Waal, 2014, p. 202). And of course the transsexual pathway now begins long before puberty, with social transition and psychological diagnosis. As de Hingh observes, "a diagnosis says you've got a problem that needs to be treated … The medical process, with pills and protocols, takes over the normal process of identification formation" (de Hingh, 2021, pp. 182–183). Clinicians need to explain how they are sure that some of the adolescents being prescribed GnRHa would not have grown into gay or lesbian adults, with their sexuality and fertility intact.

The article that introduced puberty suppression to the medical literature was accurately titled: this endocrinological intervention is designed for juvenile transsexuals (Gooren & Delemarre-van de Waal, 1996). This fact should not be obscured by claiming that puberty suppression is reversible and diagnostic. It is not diagnostic because over 95% of adolescents given GnRHa will continue to cross-sex hormones, and this fraction has not declined even as the number of youths subjected to GnRHa has multiplied by two orders of magnitude. The claim for reversibility was contradicted from the outset by the unknown effect of puberty suppression on brain development. Irreversibility has now been demonstrated by randomized control trials in non-human animals. The central justification for puberty suppression was that it increases outward resemblance to the opposite sex and requires less surgical intervention. Paradoxically, however, early puberty suppression for males will most likely make subsequent genital surgery more risky—this is what killed one of the initial Dutch cohort—with worse results.

Evidence for the benefits of puberty suppression must be acknowledged as slender. Decisions made by clinicians have prevented the collection of robust evidence. The Dutch proponents of GnRHa chose not to conduct a randomized control trial, giving two reasons (de Vries et al., 2011). Firstly, adolescents would have refused to participate, which does not make sense unless they could have obtained GnRHa from another source. Secondly, it would have been unethical to withhold GnRHa from the control group, because the clinicians believed the treatment to be beneficial—this rationale is circular because discovering whether a treatment is truly beneficial requires a randomized control trial. A lesson can be drawn from the use of GnRHa to pause precocious puberty. This was supposed to mitigate short stature, as was apparently shown by small uncontrolled studies (Hayes, 2016), but this effect was called into question by a randomized control trial (Cassio et al., 1999). When the London clinic designed a study to replicate the findings from Amsterdam, the same reasons for avoiding a randomized control study were repeated, along with an argument that subjects would soon realize whether they were receiving treatment or placebo (Viner et al., 2010). Yet this had been no impediment to the trial for children with early puberty.

The decision to rely on uncontrolled studies was exacerbated by other decisions. The Dutch clinicians chose incommensurable scales to measure gender dysphoria, which calls into question their finding that dysphoria declined following cross-sex hormones and surgery. Worse still, American clinicians eschewed the measures of psychological functioning used by the Amsterdam and London clinics (YSR, CBCL, and CGAS), thus ensuring that their tiny samples could not contribute to cumulative knowledge. One final point to remember in evaluating published studies is that the field of transgender medicine is subject to the same publication bias as every other field: unsuccessful results will not be published. This bias is illustrated by the London clinic's attempt to replicate the Amsterdam clinic's findings: the lack of improvement on GnRHa appeared in print only after the clinic was taken to the High Court of Justice for England and Wales.

While the use of GnRHa to suppress puberty helped to create the juvenile transsexual, it could now be creating another "new way of being a person" (Wren, 2020): a sexless adult. This follows from the premise that natal puberty can be a kind of disease, and therefore failure to prevent an "irreversible development of secondary sex characteristics … may be considered unethical" (de Vries et al., 2011, p. 2282). Although the Dutch protocol envisages GnRHa as a

preparatory phase before cross-sex hormones—imagined as undergoing puberty of the opposite sex—the logical conclusion is that hormones of either sex can be treated as vectors of disease. An Australian girl, Phoenix, was socially transitioned into a nonbinary identity at the age of 5 and took GnRHa from age 11. Reaching the age of 16, Phoenix refused to take testosterone because "remaining in an androgynous, peripubertal state is the only way their body can truly reflect their non-binary gender identity" (Notini et al., 2020, p. 743). The clinicians agreed to provide perpetual puberty suppression, despite the known deleterious physical effects—most obviously on bone density—and despite the unknown effects on emotional and cognitive development—which would affect Phoenix's capacity to consent. Phoenix is not the only individual seeking indefinite puberty suppression (Pang, Notini, et al., 2020). Such cases are still exceptional. But cases like FG also used to be exceptional.

Notes

1. The literature sometimes refers to GnRH (or LHRH) analogues, which is a broader classification comprising antagonists as well as agonists.
2. The pediatric endocrinologist was not named in the original article, but her identity is clear from later sources (e.g. Delemarre-van de Waal, 2014). FG is known as "B" in the published literature.
3. Bailey and Zucker (1995) had by then reviewed four additional prospective studies in the same vein as well as numerous retrospective ones. Later prospective studies demonstrated that girls who manifested cross-gender behavior as infants were also more likely to grow up as lesbian, though the association was weaker than for boys (e.g. Li et al., 2017).
4. Pediatric endocrinology's obsession with height has motivated the use of artificial estrogen to accelerate puberty in girls judged as too tall (Cohen & Cosgrove, 2009) and the use of GnRHa to delay puberty in girls judged as too short (Hayes, 2016).
5. A previous comparison (Biggs, 2020) included only 30 subjects from the London clinic and measured outcomes after 12 months. The Stata do-file is posted on Harvard dataverse at https://doi.org/10.7910/DVN/QPRCR1.
6. De Vries (2022) also cites a study from Kansas City (Allen et al., 2019) which includes an unknown number of children subjected to GnRHa before cross-sex hormones, but it took no baseline measure before puberty suppression.
7. The authors calculate the "gender diverse" proportion as 9% because they omit students who skipped the question (Kidd et al., 2021). It is more plausible to include the latter in the denominator, which yields 7%.
8. The London clinic referred a 7-year-old for endocrinological intervention, but it is not known whether GnRHa was actually prescribed before she turned 8 (Butler et al., 2022).

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