

Gender affirming hormonal treatment in Danish transgender persons: A nationwide register-based study

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Abstract

Background: Gender affirming hormonal treatment (GAHT) is a cornerstone in transgender care. National data are sparse regarding use of hormonal treatment by transgender persons.

Aim: To assess use of GAHT in transgender persons.

Design: National register-based cohort study in Danish transgender persons followed from 2000 until 2018. The main outcome measure was prescription and purchase of GAHT. Persons with ICD-10 diagnosis code of “gender identity disorder” (CGI-cohort) and persons with legal sex change but without diagnosis (CPR-cohort) were included. In the CGI-cohort, transgender women were defined by prescription of estrogen and/or cyproterone acetate and/or testosterone-5-alpha reductase inhibitors, and transgender men were defined by prescription of testosterone after study inclusion. Discontinuation of GAHT was defined as no purchase of GAHT ≥ 13 months or shift from feminizing to masculinizing hormone treatment, or vice versa.

Results: The cohort included 2789 transgender persons ($n = 1717$, CGI-cohort and $n = 1072$, CPR-cohort). The median age (interquartile range) at study inclusion was 26.1 (17.7) years for persons assigned male at birth ($n = 1447$) and 22.5 (10.5) years for persons assigned female at birth ($n = 1342$). In the CGI-cohort, the event rate for GAHT in transgender women increased from 4.0 (95% confidence interval [CI]: [3.1; 5.2]) events per 100 person in year 2000–2005 to 20.6 (17.8; 23.7) between 2014 and 2018. In transgender men, the event rate of GAHT increased from 4.2 (2.8; 6.2) to 18.8 (16.4; 21.6). The rate of discontinuation of GAHT was 0.06 (95% CI 0.049; 0.071) per person year.

Conclusions: The event rate of GAHT increased during 2000–2018. Our data suggested high adherence to GAHT.

KEYWORDS

gender affirming hormonal treatment, gender identity, morbidity, surgery, transgender

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1 | INTRODUCTION

The term transgender is used to describe individuals, whose gender identity differs from the assigned sex at birth. Transgender women (TW) are assigned male at birth (AMAB), but self-identify as women. Transgender men (TM) are assigned female at birth (AFAB), but self-identify as men.¹ Nonbinary is the most common term to describe people whose gender is not male or female.¹ Recent European studies reported that 0.7%–1.1% of people AMAB and 0.6%–0.8% of people AFAB reported incongruent gender identity.¹

Gender affirming hormone treatment (GAHT) is often a cornerstone of transgender care. Gender nonbinary people may also seek GAHT. Feminizing GAHT includes oestrogen treatment most often combined with anti-androgen treatment, and masculinizing GAHT includes testosterone treatment.^{1,2} According to Danish national guidelines, evaluation of transgender condition and initial treatment with GAHT should be prescribed by one of the three Danish centers of gender identity (CGI).³ These centers are responsible for assessment and coordination of gender affirming treatment. Maintenance treatment with GAHT may be monitored by the patient's general practitioner, but this option is rarely used due to continued need for psychological support and involvement of interdisciplinary specialists. Since 2014, legal sex-change can be performed independent of gonadectomy in Denmark.⁴ Therefore, legal sex-change is independent of contact to a CGI. The Danish National Board of Health published a national guideline in 2015, with focus on shortened evaluation period and wider access to gender affirming treatment. Transgender identity was removed from the National Board of Health's list of mental illnesses in 2016. The number of health care contacts due to gender identity related diagnoses has significantly increased during the last decade.^{1,4} The general medicine support system in Denmark reimburses a percentage of the cost for GAHT in line with all prescription drugs. Knowledge is limited regarding the prescription pattern of GAHT.⁵ The rate of discontinuation of GAHT is considered low in transgender persons,⁶ but previous studies were performed in selected study cohorts.^{5,7} Prescription and use of hormonal treatment in transgender persons without contact to a CGI remains to be determined.

In the present study, our objective was to use national registers to investigate use and adherence to GAHT in a national setting. We also investigated use of hormonal treatment in transgender persons with no contact to a CGI during the study period.

2 | MATERIAL AND METHODS

The study design was a register-based cohort study.

Study population: We included Danish transgender persons from national registers.

CGI-cohort: The study population was formed by identification of persons with ICD-10 diagnosis code of transgender as detailed below, since this would indicate contact to a CGI. Diagnosis codes are applied upon referral from the general practitioner to a CGI and reflects date of first contact at the center. Until 2017, the diagnosis codes F64-F649

("transsexual, gender identity disorder") were applied.⁸ The diagnosis codes DZ768E-DZ768E4 ("contact regarding gender identity condition") were introduced and applied after 2017. According to Danish guidelines, the CGI applied the contact diagnosis codes to all persons referred for evaluation of transgender identity. The contact diagnosis codes regarding gender identity condition are primarily used by CGI. The diagnosis code should occur during 2000–2018, and persons should have a valid Danish address at the time of inclusion. An included individual should not have a diagnosis of transgender prior to the study period. The date of study inclusion (index date) was defined as the first date for transgender diagnosis.

CPR-cohort: Persons with legal sex change were identified by change in social security number (CPR) after the age of 18 years. The Danish CPR contains 10 digits where the first six digits correspond to birth date (DDMMYY), and the last digit indicates a person's legal sex (odd digit for males, even digit for females).⁹ Legal sex change results in change of personal identification in all public systems including the public health system, tax system etc. Legal sex-change is optional, but will ensure congruence between gender identity and legal sex. According to Danish law, a citizen can apply for legal sex change after the age of 18 years, which implies change of the male or female identifier of the CPR number. Legal sex change is free of charge and can be reverted but can only be performed after 6 months of reflection time. Until 2014, legal sex change could only be performed following gonadectomy. However, since September 1st, 2014, legal sex-change can be performed independent of contact to the health care system. Persons included in the CGI-cohort were excluded from the CPR-cohort. We also excluded persons if legal sex change according to the CPR registry was reversed within 30 days. The index date was the date of CPR change.

To investigate calendar time trends, the CGI-cohort was split into sub-cohorts according to index date: 2000–2005, 2006–2009, 2010–2013, and 2014–2018. Due to limited number of study outcomes, the CPR-cohort was split according to index data 2000–2013 and 2014–2018.

2.1 | The Danish health registries

In Denmark, all citizens are provided with a unique CPR issued at birth or upon immigration to Denmark. The CPR is the key identifier in the Danish population-based medical records and can link data from all Danish health and social care registers at an individual level.^{10,11} Information regarding hospital contacts was included from all persons along with dates of death if applicable. We used data from the National Patient Register¹⁰ and Civil Registration System.¹¹ The Civil Registration System was established in 1968 and maintains complete records of births, deaths, civil, and emigration status. The Civil Registration System contributed data on death and emigration during follow-up, civil status, and geographic origin.¹¹

ICD-10 diagnosis codes: The National Patient Register contains data on all inpatient hospital contacts in Denmark since 1977, and outpatient contacts are included since 1995.⁹ From 2002, the National

Patient Register also includes contacts for private hospitals excluding private practice specialists and general practitioners. We extracted ICD-10 diagnosis codes of transgender from 2000–2018. Diagnoses were extracted from psychiatric and somatic parts of the National Patient Register.

Sex change: We used the Civil Registration System to define sex change.

Medicine prescriptions: Information on all prescriptions issued by prescribers, general practitioners, or specialists in Denmark from 1995 to 2018 was retrieved from the National Prescriptions Registry.¹² The National Prescriptions Registry database contains a complete record of Anatomic Therapeutic Chemical code, date drug dispensed, and number of drug packets for all prescriptions filled at Danish pharmacies.

2.2 | Definition of study parameters

2.2.1 | Age was calculated at the index date

Assigned sex at birth was determined as the earliest recorded CPR-encoded sex. Transgender persons were divided into persons affirmed male sex at birth (AMAB, which would most often be TW) and persons assigned female sex at birth (AFAB, which would most often be TM). The CPR number is issued at birth or when immigrating to Denmark. In the present study, misclassification of sex at birth in the CGI-group would occur if a person immigrated to Denmark after sex change. Furthermore, misclassification might occur if an individual received a transgender diagnosis or had legal sex change performed before year 2000. Persons with prescription of intrauterine device (G02BA) were named AFAB.

The event of GAHT was defined as prescription followed by at least one purchase of feminizing and/or masculinizing treatment in the period from January 1st 2000 to December 31st 2018 following the index date. Our definition of feminizing treatment was based on European and Danish guidelines.^{2,3,13} Feminizing treatment was defined as prescription of systemic estrogen (estradiol G03CA03, estriol G03CA04) and/or cyproterone acetate (G03HA01) and/or testosterone-5-alpha reductase inhibitors (finasteride G04CB01, dutasteride G04CB02). Masculinizing treatment was defined as prescription of testosterone (G03BA03). In Denmark, GnRH analogue is predominantly used to block puberty in transgender persons <18 years, and the drug is administered without prescription by the specialized center for growth and reproduction located in Copenhagen.² As a result, data regarding use of GnRH analogue in transgender adolescents cannot be extracted from Danish registers. GnRH treatment for adult transgender persons is generally not available in Denmark.²

Adjunctive treatment: Spironolactone (C03DA01) is prescribed not only in transgender persons, but is also prescribed as antihypertensive treatment or for treatment of hirsutism. Therefore, use of spironolactone was investigated as separate outcome. Prescription of progestogen (G03D, G03AC) and oral contraceptive containing progestogen

and estrogen (G03AB, G03F) and cyproterone acetate and estrogen (G03HB) is not part of recommendations for GAHT¹³ and was investigated as separate outcome.

TW and TM were defined according to their first prescription of GAHT within 5 years after the index date. TW were persons with ≥ 1 prescription of feminizing treatment and TM were persons with ≥ 1 prescription of masculinizing treatment. Some persons in the CGI-cohort and the CPR-cohort did not have prescriptions of GAHT. Persons without prescription of GAHT were named according to their assigned sex at birth: Persons AMAB were named TW, and persons AFAB were named TM.

Discontinuation of GAHT in the CGI-cohort was defined as no purchase of GAHT ≥ 13 months or shift from feminizing treatment to masculinizing treatment or vice versa after the index date. The chosen cut point at 13 months reflected that Danish patients usually attend annual follow-up. However, medicine prescriptions have a validity of 2 years, and we also investigated the number of persons with no purchase of GAHT ≥ 24 months. We divided persons with discontinuation of GAHT according to assigned sex at birth and index age \leq and >25 years.

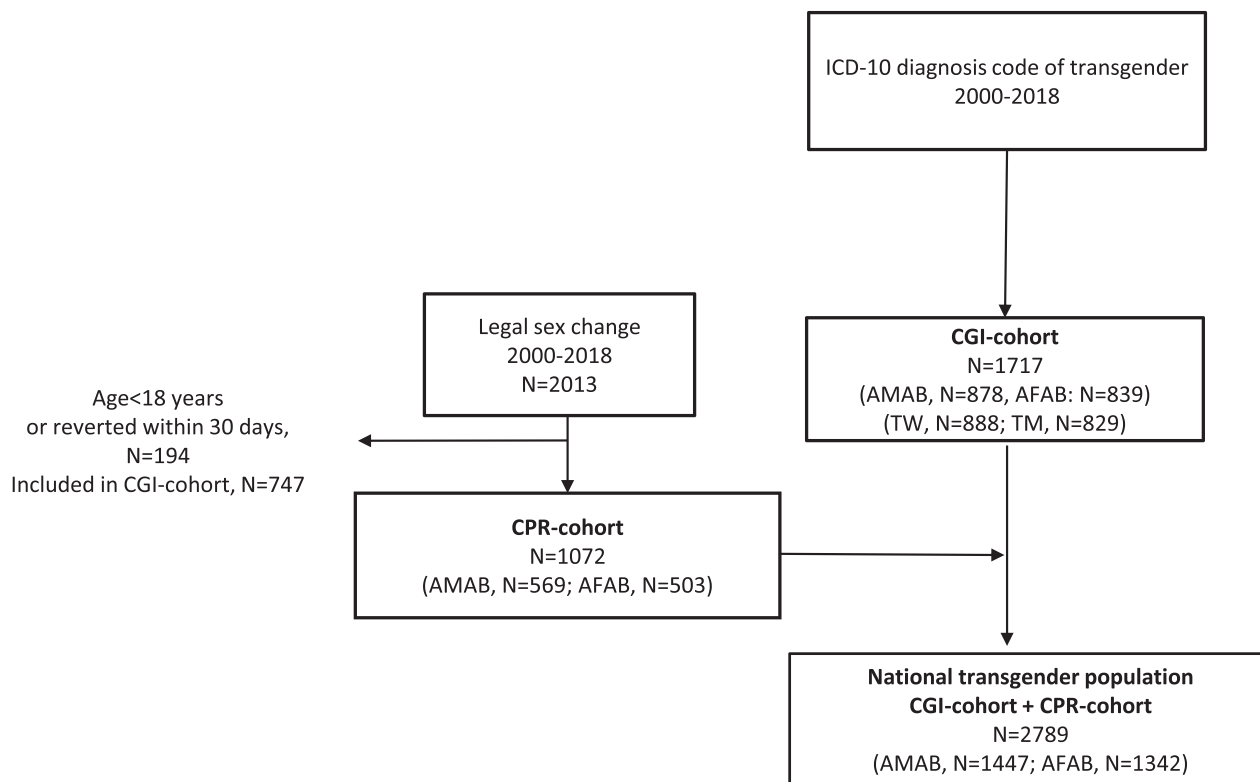
2.3 | Ethics

The study design was an open register-based cohort study, and no approval was necessary from the local Ethics committee or Institutional Review Board by Danish law. The study was approved by the Data Protection Agency and Statistics Denmark. Information regarding the study is published with OPEN ID: 939 <https://open.rsyd.dk/OpenProjects/openProject.jsp?openNo=939&lang=da>

2.4 | Statistical analyses

Baseline characteristics in transgender persons are presented as frequencies for categorical variables. Continuous variables are summarized as medians with interquartile range. When estimating the prevalence of GAHT, the time from inclusion until first purchase was recorded as censoring at the end of follow-up or emigration. The prevalence of GAHT was then estimated as the cumulative incidence at 2 or 3 years from entry into the cohort by the Aalen-Johansen estimator treating death as a competing risk. When discontinuation of GAHT was estimated, an individual was perceived as being at risk following their first GAHT redemption. Crude purchase and discontinuation rates of GAHT were estimated as the number of events per person-time calculating confidence intervals in the Poisson model on the logarithmic scale and then back-transforming. Death was not counted as discontinuation of GAHT. Death was included in analysis in the sense that persons who died no longer contributed with risk time.

Data management and data analyses were conducted using Stata 16 (StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC) through a remote VPN access to Statistics Denmark with analysts blinded to the personal identities of the study subjects.



Persons included in CPR-alone cohort had no ICD-10 diagnosis code of transgender (see text for details)

AMAB: Assigned male at birth, AFAB: Assigned female at birth

TW: Transgender female, TM: transgender male

CPR: Social security number, CGI: Center of gender identity

FIGURE 1 Flowchart of included study population

2.5 | Sensitivity analysis

We performed a sensitivity analysis in the CPR-cohort, as persons in this cohort had no contact to a Danish CGI within the study period (2000–2018).

3 | RESULTS

A flowchart of the national transgender population is shown in Figure 1.

The CGI-cohort included 1717 individuals. In the CGI-cohort, 878 (51%) were AMAB, and 839 (49%) were AFAB. The median age at the index date was 26.2 years in AMAB individuals and 19.8 years in AFAB individuals (Table 1).

Legal sex change was performed in 2013 individuals. We excluded 194 individuals with age <18 years or reverted CPR change within 30 days. A total of 747 persons were already included in the CGI-cohort, which left 1072 persons in the CPR-cohort (Figure 1); 569 AMAB (53%) and 503 (47%) AFAB with median age 26.0 and 26.3 years, respectively. The median age at study inclusion decreased from 28.5 to 22.8 years for persons AMAB and from 20.8 to 18.5 years for persons AFAB during the time period 2000–2016 versus 2017–2018.

Hormone use in the CGI-cohort is presented in Table 2 (TW, $N = 888$, TM, $N = 829$). In TW, estrogen was purchased by 398 persons (median age 31.6 years at inclusion), and cyproterone acetate was purchased by 275 persons. In TM, testosterone was purchased by 347 persons (median age 20.8 years).

The event rate for GAHT increased from 4.0 (95% confidence interval [CI]: [3.1; 5.2]) events per 100 person years during year 2000–2006 to 20.6 [17.8; 23.7] during year 2014–2018 in TW individuals (Table 3). In TM individuals, the corresponding event rates for GAHT increased from 4.2 [2.8; 6.2] to 18.8 [16.4; 21.6]. Higher cumulative incidence of GAHT according to more recent index date is shown in Figure 2. Table 3 reports the 2- and 3-year cumulative incidences with confidence interval.

Discontinuation of GAHT. The number of events for discontinuation of GAHT was 108 during 1844 person years, which corresponded to an event rate of 0.059 CI (0.049; 0.071). We stratified the event of GAHT discontinuation by index year (before and after year 2014). Prior to 2014, the event rate was 99 per 1352 person years (event rate 0.073 [0.060; 0.089]). In the period following January 1st 2014, the event rate was 9 in 492 person years (event rate 0.018 [0.010; 0.035]).

Event of GAHT discontinuation was stratified by index age (< vs. ≥ 25 years) and birth assigned sex (AMAB vs. AFAB). The rate of

TABLE 1 Description of transgender study cohort (n = 2770)

	Total N	Assigned male at birth		Assigned female at birth	
		N	Age median (IQR)	N	Age median (IQR)
Total, CGI-cohort	1717	878	26.2 (22.1)	839	19.8 (9.1)
2000–2016	1110	618	28.5 (24.0)	492	20.8 (10.9)
2017–2018	607	260	22.8 (12.6)	347	18.5 (6.5)
CPR-cohort (legal sex change alone)	1072	569	26.0 (12.3)	503	26.3 (9.1)
National transgender population CGI-cohort + CPR-cohort	2789	1447	26.1 (17.7)	1342	22.5 (10.5)

Note: Data presented as number.

Abbreviations: CGI, centre of gender identity; CPR, social security number; IQR, interquartile range.

TABLE 2 Use of hormone treatment in center of gender identity (CGI)-cohort (n = 1717)

	Total N	TW N = 888		TM N = 829	
		N (%)	Age median (IQR)	N (%)	Age median (IQR)
GAHT, ATC code					
Testosterone G03BA03	347 α	≤5	.	347 (100.0) α	20.8 (7.9)
Estrogen G03CA03, G03CA04	398	391 (98.2)	31.6 (24.8)	7 (1.8)	44.3 (23.3)
Cyproterone G03HA01	275 α	275 (100.0) α	28.0 (22.9)	≤5	.
5 α -reductase inhibitor G04CB01 G04CB02	22 α	22 (100.0) α	52.8 (30.8)	≤5	.
Adjunctive treatment, ATC code					
Spironolactone C03DA01	44 α	44 (100.0) α	45.7 (30.1)	≤5	.
Progestogen G03D, G03AC	66	14 (21.2)	42.5 (19.1)	52 (78.8)	19.1 (8.1)
Oral contraceptive G03AB, G03HB, G03F	24	15 (62.5)	36.8 (12.8)	9 (37.5)	26.0 (5.4)

Note: Redemption of hormone treatment in CGI-cohort during follow-up. An individual may contribute to multiple rows in the table but can only contribute once per row. GAHT was defined as purchase (redemption) of natural estrogen and/or cyproterone and/or 5 α -reductase inhibitor treatment and/or testosterone. Patients were divided in TW and TM according to first redemption of GAHT. See Method section for details. Use of adjunctive treatment is presented in lower part of table.

Age refers to age at study inclusion.

α : Exact total N and exact row percentage cannot be calculated due to discretized values ≤5. In these cases, the discretized value has been set to the value zero.

Abbreviations: ATC, anatomical therapeutic chemical; GAHT, gender affirming hormone treatment; IQR, interquartile range; TM, transgender man; TW, transgender woman.

discontinuation of GAHT in persons < 25 years was 0.058 (0.035; 0.094) in AMAB and 0.040 (0.026; 0.063) in AFAB. The corresponding rates in persons ≥25 years were 0.072 (0.055; 0.093) in AMAB and 0.056 (0.035; 0.088) in AFAB.

The number of events with no purchase of GAHT ≥24 months was 72 during 1993 person years (rate 0.036 [0.029; 0.046]).

3.1 | Sensitivity analysis

We investigated the use of hormonal treatment the CPR-cohort (Table A1). In AMAB, estrogen was prescribed and purchased in 80 persons, and cyproterone was prescribed in 14 persons. In AFAB, testosterone was prescribed in 32 persons. The cumulative incidence of GAHT in the CPR-cohort is presented in Appendix, Figure 2 where persons were divided according to assigned sex at birth (AFAB/AMAB) and index year (before/after 2014).

4 | DISCUSSION

In this unique register-based study, we described use of GAHT in transgender persons in a Danish national setting. Our data showed higher rate of use of GAHT and shortened time from the index date to purchase of GAHT during our observation period (year 2000–2018). We found that the rate of discontinuation of GAHT continued to be low despite shortened time to first purchase of GAHT. Furthermore, we were able to investigate use of hormonal treatment in transgender persons without contact to a CGI. We found that 38% transgender persons had no contact to a CGI during the study period, and use of hormonal treatment in persons without contact to a CGI was low.

In the present study, the incidence rates for first purchase of GAHT increased around four-fold during the study period, which suggested shortened period from referral to CGI to start of GAHT and the cumulative incidence of prescription of GAHT at 3 years following diagnosis

TABLE 3 Incidence rates of gender affirming hormone treatment after study inclusion in center of gender identity (CGI)-cohort (n = 1700)

	Gender affirming hormone treatment				
	Person-years	Events	Rate per 100 person years (95% CI)	Two-year cumulative incidence (95% CI)	Three-year cumulative incidence (95% CI)
TWN = 877					
2000–2005	1432.66	57	4.0 (3.1; 5.2)	13.5% (8.5; 19.7)	20.7% (14.4; 27.7)
2006–2009	783.16	58	7.4 (5.7; 9.6)	16.3% (10.1; 23.8)	19.1% (12.4; 26.9)
2010–2013	814.05	102	12.5 (10.3; 15.2)	15.2% (10.4; 20.7)	26.7% (20.5; 33.2)
2014–2018	904.76	186	20.6 (17.8; 23.7)	33.7% (29.0; 38.5)	46.8% (41.1; 52.2)
Total	3934.63	403	10.2 (9.3; 11.3)	23.5% (20.7; 26.4)	33.2% (29.9; 36.6)
TMN = 823					
2000–2005	601.33	25	4.2 (2.8; 6.2)	1.8% (0.1; 8.5)	1.8% (0.1; 8.5)
2006–2009	467.74	31	6.6 (4.7; 9.4)	1.7% (0.1; 8.0)	1.7% (0.1; 8.0)
2010–2013	781.40	93	11.9 (9.7; 14.6)	8.4% (4.8; 13.3)	23.6% (17.4; 30.3)
2014–2018	1072.62	202	18.8 (16.4; 21.6)	31.5% (27.1; 35.9)	47.4% (41.9; 52.6)
Total	2923.10	351	12.0 (10.8; 13.3)	21.4% (18.5; 24.5)	33.6% (30.0; 37.3)

Note: Incidence rates of first purchase of gender affirming hormone treatment after study inclusion.

Abbreviations: CI, confidence interval; TW, transgender woman; TM, transgender man.

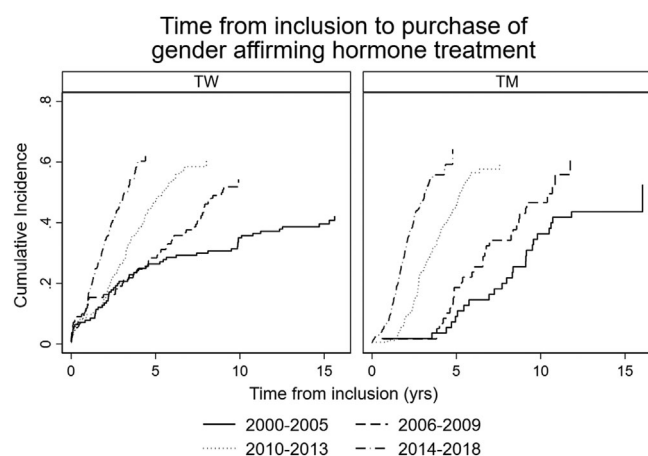


FIGURE 2 Event rate for first use of gender affirming hormonal treatment (GAHT) after study inclusion in the center of gender identity (CGI)-cohort divided according to index year. TM, transgender men; TW, transgender women

increased to more than 45% in the sub-cohort included during 2014–2018. In accordance, recent studies reported that wish for hormone management was one of the primary aims for seeking health care programs in transgender study cohorts.^{14,15} The present data are in agreement with recent publications showing increasing number of health care contacts regarding gender affirming treatment,^{4,16} and present ratio of persons AMAB/AFAB seeking medical care is around one.⁴ We are not aware of other national studies regarding changes in prescription pattern of GAHT. However, Wiepjes et al. investigated the use of GAHT and risk of regret in 6793 transgender persons at a CGI in Amsterdam, which was responsible for treatment of more than 95% Dutch transgender persons⁵; in accordance with the present study, the age at referral decreased during the observation period.⁵ However, in

contrast to our findings, the percentage of persons initiating GAHT within 5 years after referral decreased during the observation period (1972–2014) from nearly 100% to around 70%.⁵ The inclusion period of the present study started in 2000, whereas Wiepjes et al. did not include more recent years. Furthermore, national health guidelines in Denmark and Holland differ regarding gender affirming surgical treatment. Upper surgery without GAHT is not usually performed according to Danish guidelines, whereas this was allowed in the Netherlands⁵; accordingly, more nonbinary persons without wish for GAHT could be included in the Dutch study cohort.⁵ It is also possible that decreasing incidence rate of GAHT in the Dutch study could reflect referral of persons with other forms of gender dysphoria, where GAHT is not requested.⁵ The time from referral to first GAHT purchase is highly influenced by the health capacity, as the waiting list for first evaluation at gender teams in Danish CGIs is growing. Limited capacity of the general health system in Denmark will affect results of future studies with expected longer duration from referral to prescription of GAHT.

The adherence to GAHT was high, and we found no indication of higher risk of discontinuation of GAHT despite shorter duration from the index date to first prescription of GAHT. Recently, gender affirming treatment of young individuals is debated,¹⁷ and some CGI centers have stopped gender affirming treatment in persons below 25 years of age. Our data did not suggest a higher rate of GAHT discontinuation in persons <25 years, and the highest rate of discontinuation was found in AMAB ≥ 25 years. Our dataset was unique, as we could evaluate use of GAHT independent of attendance to a CGI. Therefore, information regarding use of GAHT was available in patients, who could be lost to follow-up in other studies. Few studies evaluated discontinuation of GAHT,^{18–20} and more data are highly needed. Results from the US Transgender survey showed that 13.1% of persons pursuing gender affirmation had a history of regret.¹⁹ These results contrast studies reporting risk of regret <1% in other transgender

study populations.^{5,21} However, regret in these studies was defined as detransition after gender affirming lower surgery,⁵ which would represent a selected study cohort of transgender persons. More studies are needed to determine if subsets of transgender persons are in higher risk of discontinuation of GAHT and also the reasons for terminating GAHT, in order to optimize care for transpersons.

Cyproterone acetate was the most commonly prescribed androgen blocker in the present study. These data expand findings from a recent questionnaire-based study regarding the use of feminizing treatment in the Nordic countries, where cyproterone acetate was prescribed in >40% TW and < 10% were treated with spironolactone.³ The paper did not include prescription data, but included answers from medical professionals at the three Danish CGI regarding preferred treatment regimens.³ Testosterone levels are higher with spironolactone than with cyproterone acetate treatment,²² but adverse effects of cyproterone acetate on lipid profiles, coagulation system, and risk of meningioma are well described.² At present, studies regarding the lowest effective dosage of cyproterone acetate are ongoing.^{23,24} The optimal use of androgen blockers in TW is debated,² and the present study design will allow us to investigate the risk of short and long-term adverse effects of GAHT. The present study is valuable for future long-term studies of GAHT including possible side effects of hormone treatment, effects on reproductive health, and overall health.

The cumulative incidence of GAHT was low in the CPR-cohort, especially from 2014 onwards. In accordance, Danish national guidelines define gender-affirming treatment as highly specialized treatment, which should be initiated by gender teams at CGI. According to the study design, persons in the CPR-cohort had no contact to CGI during 2000–2018, but some persons may initiate GAHT before this period and could be monitored outside a CGI, that is, at a general practitioner or private specialist. Our data supported that the number of transgender persons treated with GAHT outside the setting of a Danish CGI is low. A few persons, AMAB, received oral contraceptive pills, which is not considered gold standard feminizing treatment.² GAHT can be self-prescribed and purchased on the internet, which would not be detected in the current study setting. The rate of self-prescribed use of GAHT could be considerable.¹⁵ Prospective health may be affected by self-prescribed use of GAHT, and we plan to compare long-term mortality and morbidity in the CGI-cohort and CPR-cohort in future studies.

Strengths and limitations may apply to the present study. Important strengths of the study are nationwide data and the possibility to link data regarding GAHT on individual basis. The inclusion of persons with legal sex change allowed us to investigate the use of prescribed sex steroid hormones in persons without contact to CGI. Some limitations may apply to the present study. We obtained transgender diagnosis by available ICD-10 codes and CPR changes. As a result, transgender persons without hospital contacts and/or persons with no wish for CPR change would not be included in the dataset. The present study cohort will represent a selected study cohort of transgender individuals, and the present study findings may not translate into nonbinary persons. Furthermore, persons who terminated transgender care at a CGI before year 2000 would be left outside the dataset. Relative strict

criteria of GAHT were applied in the present study, which could lead to underestimation of use of GAHT. Furthermore, Denmark has good access to health care, but transgender persons with self-prescribed use of sex hormones could not be evaluated by register-based data. In Denmark, change of CPR is rarely performed, except for transgender persons. Protection of persecuted persons could also allow CPR change, but these cases will not usually involve change of the sex-identifier of the CPR number. We divided persons according to assigned sex at birth, which could lead to misclassification of sex in foreigners if they immigrated to Denmark after the date of the legal sex change. Therefore, we applied the use of feminising or masculinizing hormonal treatment as an additional criterion to define TW and TM. However, due to this study design, self-identified gender was more likely to be correctly defined in individuals, who entered the study cohort early. Similarly, the CPR-cohort was defined by conditioning on the future, that is, that the individual did not enter the CGI-cohort during the study period. CPR-change imply 6-month reflection time, and the dataset would miss persons who wish to make legal sex change, but have not yet done so. Discontinuation of GAHT was defined according to redemption databases, which imply methodological challenges.²⁵ Furthermore, follow-up duration was relatively limited in this study, which would affect study results.

4.1 | Perspective

In the present study, we showed higher event rate of the use of GAHT during year 2000–2018 and high adherence to GAHT. The use of prescribed hormonal treatment in transgender persons without contact to a CGI was limited. Future studies will be able to bring knowledge regarding long-term health during GAHT.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

AUTHOR CONTRIBUTIONS

Idea, design, and writing manuscript: Dorte Glintborg and Marianne Skovsager Andersen. Design, data analysis, and criticism of manuscript: Katrine Hass Rubin. Design, data analysis, and writing manuscript: Simon Bang Kristensen. Idea and criticism of manuscript: Øjvind Lidegaard, Guy T'Sjoen, and Malene Hilden.

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APPENDIX

Figure A1 and Table A1

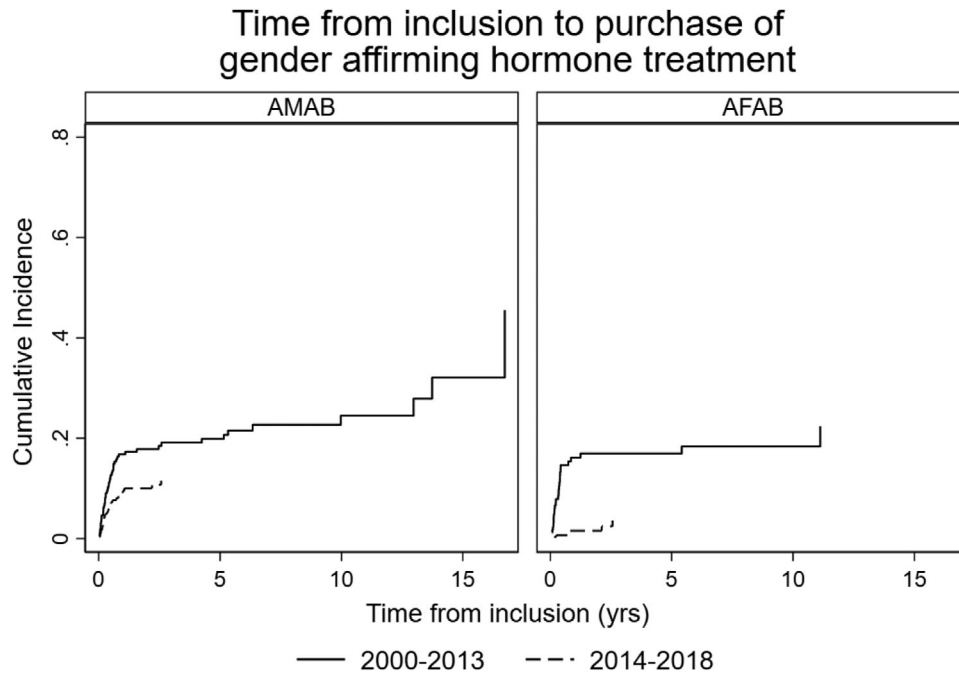


FIGURE A1 Cumulative incidence of gender affirming hormone treatment in CPR-cohort. Cumulative incidence of use gender affirming hormone treatment (prescription and purchase) in CPR-cohort split according to index date: 2000–2014 and 2014–2018. AFAB, assigned female at birth; AMAB, assigned male at birth

TABLE A1 Use of hormone treatment in CPR-cohort

	Total N	Assigned male at birth N = 569		Assigned female at birth N = 503	
		N (%)	Age median (IQR)	N (%)	Age median (IQR)
GAHT, ATC code					
Testosterone G03BA03	32 α	≤5	.	32 (100.0) α	30.8 (8.2)
Estrogen G03CA03, G03CA04	80 α	80 (100.0) α	41.8 (22.6)	≤5	.
Cyproterone G03HA01	14 α	14 (100.0) α	39.1 (30.1)	≤5	.
5 α -reductase inhibitor G04CB01 G04CB02	0 α	≤5	.	≤5	.
Adjunctive treatment, ATC code					
Spironolactone C03DA01	8 α	8 (100.0) α	44.2 (14.4)	≤5	.
Progestogen G03D, G03AC	31 α	31 (100.0) α	25.4 (7.3)	≤5	.
Oral contraceptive G03AB, G03HB, G03F	25 α	25 (100.0) α	25.7 (11.4)	≤5	.

Note: Prescription and use (redemption) of hormone treatment in CPR-cohort. An individual may contribute to multiple rows in the table, but can only contribute once per row. Persons divided according to assigned gender at birth. GAHT was defined as purchase of natural estrogen and/or cyproterone and/or 5 α -reductase inhibitor treatment and/or testosterone. Use of adjunctive treatment is presented in lower part of table.

Abbreviations: ATC, anatomical therapeutic chemical; GAHT, gender affirming hormone treatment; IQR, interquartile range.

Age refers to age at study inclusion.

α : Exact total N and exact row percentage cannot be calculated due to discretized values ≤5. In these cases, the discretized value has been set to the value zero.