AALBORG UNIVERSITY

COMPREHENSIVE UNDERSTANDING OF TRANSGENDER EXPERIENCES: COHORT DEVELOPMENT AND THE IMPACT OF GENDER-AFFIRMING HORMONE THERAPY ON QUALITY OF LIFE

Written by:
Emma Elisabeth Skovby Petersen
Frederika Paula Tyn Kiy

Supervisor:
Ulrik Schiøler Kesmodel

May 31st 2024

Department of Health Science and Technology

Medicine with Industrial Specialisation (Translational Medicine)
Selma Lagerløfs Vej 249
9260 Gistrup

inst.hst@hst.aau.dk

Project Title: Comprehensive Understanding of Transgender Experiences: Cohort Development and the Impact of Gender-Affirming Hormone Therapy on Quality of Life

Project Theme: Transgender and Gender-Diverse Individuals and Their Quality of Life

Project: Master's Thesis (9th and 10th semester)

Project Period: September 1, 2023, to May 31, 2024

Project Group: 9033

Supervisor:

Ulrik Schiøler Kesmodel, Clinical Professor, Department of Obstetrics and Gynaecology, Aalborg University Hospital

Pages/characters: 18 / 43.068

Appendix: 1 page

Compiled by:

Emma Elisabeth Skovby Petersen
20193680

Frederika Paula Tyn Kiy
20194965

Preface

This project was carried out in collaboration with the Centre for Gender Identity at Aalborg University Hospital, Denmark, during the period from September 1, 2023, to May 31, 2024. This project was written by Emma Elisabeth Skovby Petersen and Frederika Paula Tyn Kiy and supervised by Ulrik Schiøler Kesmodel.

Acknowledgement

List of Abbreviations

AFAB - Assigned Female At Birth

AMAB - Assigned Male At Birth

AQ - Autism Spectrum Quotient

CGI - Centre for Gender Identity

D1 - Physical Domain of the WHOQOL-BREF

D2 - Psychological Domain of the WHOQOL-BREF

D3 - Social Domain of the WHOQOL-BREF

D4 - Environmental Domain of the WHOQOL-BREF

EDE-Q - Eating Disorders Examination Questionnaire

GAHT - Gender-Affirming Hormone Therapy

GAS - Gender-Affirming Surgery

GDPR - General Data Protection Regulation

GMSRM - Gender Minority Stress and Resilience Measure

MANOVA - Multivariate Analysis of Variance

SAP – Statistical Analysis Plan

TCS - Transgender Congruence Scale

TGD - Transgender and Gender-Diverse

TM - Transgender Men

TraCK - Transkohorte ved Center for Kønsidentitet (Transgender Cohort at the Centre for Gender Identity)

TW - Transgender Women

QoL - Quality of Life

WHOQOL-BREF - World Health Organization Quality of Life Brief Version

Abstract

Background: Transgender and gender-diverse (TGD) individuals experience various challenges, including mental health issues and barriers to healthcare access. In addition, TGD individuals also report lower Quality of Life (QoL) levels compared to cisgender individuals. A common intervention shown to have a positive effect on mental well-being and QoL of TGD individuals is gender-affirming hormone therapy (GAHT). However, the short- and long-term effects of GAHT are not fully understood. Therefore, this study aimed to establish a comprehensive database of TGD individuals and to investigate QoL between patients receiving GAHT and controls for both patients assigned male at birth (AMAB) and patients assigned female at birth (AFAB). In addition, QoL between patients AMAB and patients AFAB was investigated. Furthermore, this study aimed to investigate the relationship between sex hormone levels and QoL.

Method: This study consists of two parts: 1) the development of a transgender cohort and 2) the original study. A Transgender Cohort at the Centre for Gender Identity (TraCK), Aalborg University Hospital, was established in REDCap, which included self-reported questionnaires and information from medical records. The original study used a cross-sectional study design, and patients included in the study were recruited from the TraCK between February 14 and May 6, 2024. To measure QoL the WHOQOL-BREF questionnaire was used to investigate four QoL domains. MANOVA and t-tests were performed to investigate QoL between patients receiving GAHT and controls for both patients AMAB and patients AFAB, and QoL between assigned sex at birth groups. Additionally, linear regression analyses were performed to investigate the relationship between QoL and levels of oestradiol and testosterone for patients AMAB and patients AFAB, respectively.

Results: 424 patients were included in the TraCK until May 6, 2024, however, only 372 patients completed all questionnaires. In the original study, 360 patients were included (169 AMAB and 191 AFAB). A statistically significant difference in QoL was found between patients receiving GAHT and controls for both patients AMAB ($p = 0.005$) and patients AFAB ($p = 0.021$). A statistically significantly higher mean QoL score of the psychological domain (D2) was found for both patients AMAB and patients AFAB ($p = 0.003$; $p = 0.004$, respectively). Between patients AMAB and patients AFAB a statistically significant difference in QoL was found for both the GAHT- and control group ($p = 0.010$; $p = 0.042$, respectively). However, only a significantly higher mean QoL score of the social domain (D3) was found for patients AFAB compared to patients AMAB in the GAHT group. No significant linear relationship was found between sex hormone levels and QoL.

Conclusion: It was possible to establish a comprehensive database of TGD patients. This study found that QoL for patients receiving GAHT was statistically significantly higher than for controls, especially for the psychological domain. Also, a higher QoL was found for patients AFAB compared to patients AMAB, specifically for the social domain. This study highlights the advantages of offering GAHT to TGD individuals and differences between assigned sex at birth. However, future longitudinal studies are crucial to investigate the short- and long-term effects of GAHT.

Table of Contents

1. Introduction

Transgender and gender-diverse (TGD) individuals are terms used to describe people whose gender identity does not align with their assigned sex at birth.[1] The prevalence of TGD individuals is estimated to be 0.54-1.1% of the world's population.[2–5]

TGD individuals often face a variety of challenges in their daily lives including mental health problems, discrimination, prejudice, and minority stress.[6–8] Several studies have found that TGD individuals have a higher prevalence of psychiatric disorders including depression, anxiety as well as eating disorders compared to the cisgender population.[6,9,10] The high prevalence of mental health problems among TGD individuals could be due to a combination of social discrimination and self-criticism regarding body dissatisfaction and self-acceptance.[11] To increase their self-acceptance and to relieve gender incongruence TGD individuals often seek gender-affirming hormone therapy (GAHT) either from healthcare providers or other resources.[12–14] A possible explanation for why TGD individuals seek GAHT from other resources could be multiple barriers to healthcare including long waiting times, under-resourced healthcare systems, lack of competent healthcare providers, and prejudgments from healthcare providers.[15,16] This aligns with the findings from studies by Mepham et al. 2014 and Pop et al. 2022 where self-medication practices were found to be common among TGD individuals.[13,14] However, those who self-medicate may be less aware of possible side effects than those who seek GAHT from healthcare providers.[13,14] Altogether, these challenges illustrate that there is a need for comprehensive treatment of all aspects of gender incongruence among TGD individuals.

Gender-affirmative health care is often provided by a multidisciplinary team focusing on social, psychological, behavioural, and medical aspects.[17–19] The treatment regimen of TGD individuals encompasses psychological support, gender-affirming voice training, laser hair removal, GAHT, and gender-affirming surgery (GAS).[20–22] Of these treatment options, GAHT is the most common medical treatment among TGD individuals to help the transitioning process and consists of either feminizing or masculinizing GAHT.[22–24] Feminizing GAHT often includes natural oestrogen alongside testosterone-blocking treatment, whereas masculinizing GAHT only requires testosterone supplementation.[25–29]

Overall, the purpose of GAHT is to achieve a reduction of endogenous sex hormone levels to induce a decline in secondary sex characteristics, and to substitute exogenous sex hormones that match the individual's gender identity.[30] The desired effects of feminizing GAHT occur by a stimulation of secondary sex characteristics thereby inducing breast growth, fat redistribution at the hips, softening of the skin, and a reduction in body hair growth.[28,30] Opposed to feminizing GAHT, masculinizing GAHT aims to stimulate facial and body hair growth, deepen the voice, increase muscle mass, and induce amenorrhea.[30,31] Beyond these desired effects of GAHT, there is a risk of side effects. Regarding feminizing GAHT side effects may include mood swings, reduced libido, weight gain, cardiovascular diseases, and venous thrombosis.[32,33] Some of the most common side effects of masculinizing GAHT encompasses acne, alopecia, erythrocytosis, sleep apnoea, and hypertension.[30,32] Nonetheless, a knowledge gap remains regarding the short- and long-term treatment effects of GAHT.[34–36]

As it is widely recognized that sex hormones influence mental health factors such as fatigue, behaviour, mood, and stress, it is conceivable that GAHT may have similar effects. [37,38] Sex hormones play a crucial role in brain function by the modulation of neurotransmitters, thus influencing mental factors.[37,38] Notably, a study has found that feminizing GAHT has negative effects on these mental factors, whereas masculinizing GAHT has beneficial effects.[37] As sex hormones affect brain function and subsequently affect mental well-being, it implies a potential relationship between sex hormone levels and the Quality of Life (QoL).[39–41]

QoL can be influenced by physical and psychological well-being, as well as social and environmental factors.[42] Physical well-being depends on factors such as energy, mobility, sleep, pain, and the ability to perform daily activities. Psychological well-being covers for example self-esteem, self-image, mentality, mental status, negative thoughts, and positive attitudes. Social factors comprise social support and relationships. Environmental factors include safety, financial resources, the general environment, and access to health and social services.[42]

Several studies indicate that TGD individuals have a lower QoL across various aspects compared to cisgender individuals.[43–45] Nonetheless, studies suggest that GAHT may improve the QoL of TGD individuals.[23,46–48] Possible reasons for this could be the GAHT-induced changes which strengthen gender affirmation, boost self-esteem, and lead to an increased social acceptance, and psychological well-being.[22,49–51] Thus, it is important to investigate the QoL of TGD individuals

in relation to GAHT and the potential relationship between sex hormone levels and QoL. However, a systematic literature search performed by the authors revealed a knowledge gap within this field with only limited research of low evidence regarding the relationship between GAHT and QoL.

This illustrates that addressing their challenges and providing appropriate treatment for TGD individuals is crucial. Nevertheless, there remains a lack of evidence regarding the short- and long-term treatment effects, emphasizing the need for comprehensive, large-scale prospective cohort studies. With an expanded understanding of the challenges and treatment effects, healthcare professionals can offer evidence-based recommendations that may significantly impact the QoL, mental well-being, as well as physical health, and social relationships of TGD individuals.

Hence, to provide a systematic overview of TGD individuals regarding psychological and physiological treatment effects, a comprehensive database on TGD individuals was developed. This database is intended to form the foundation for future research. Thus, data from this database were used to investigate the second aim of this study.

1.1 Aims

1. To develop a large transgender cohort using a web-based platform
2. Aims for the original study:
   - To investigate the relationship between GAHT and QoL for both patients assigned male at birth (AMAB) and patients assigned female at birth (AFAB)
   - To investigate the difference in QoL between patients AMAB and patients AFAB
   - To investigate the relationship between QoL and sex hormone levels of oestradiol and testosterone of patients AMAB and patients AFAB, respectively
   - To investigate whether time in GAHT, type of medication, age, and GAS affect the relationship between GAHT and QoL

2. Methods

2.1 Development of a Database

A Transgender Cohort (TraCK; Transkohorte ved Center for Kønsidentitet) was developed in a multidisciplinary collaboration with the Centre for Gender Identity (CGI), Department of Obstetrics and Gynaecology, Department of Endocrinology and the Psychiatric Research Unit at Aalborg University Hospital, Denmark. The TraCK is a single-centre cohort with retro- and prospective data.

2.1.1 Cohort Population

The cohort population encompasses TGD individuals referred to the CGI, for evaluation of gender incongruence, during the period between 2017 and 2028. The patients are recruited by invitation via the Danish authorities' digital mailbox called e-Boks from February 14, 2024, until July 31, 2028. To participate in the cohort patients must provide informed consent and complete questionnaires at enrolment. A participation rate of 50% is expected, which will result in 1000 patients being enrolled in this cohort over five years.

2.1.2 Outcome Data

This cohort contains comprehensive data collected from both self-reported questionnaires and medical records from psychologists, psychiatrists, gynaecologists, endocrinologists, and other specialists if appropriate and relevant e.g. otorhinolaryngologists.

At baseline six self-reported questionnaires are included consisting of one self-developed questionnaire and five validated questionnaires in Danish. The self-developed questionnaire examines key factors such as demographics, gender identity, lifestyle, mental well-being, and physical health. The five validated, self-reported questionnaires comprise the World Health Organization Quality of Life Brief Version (WHOQOL-BREF),[52] Eating Disorders Examination Questionnaire (EDE-Q),[53] Autism Spectrum Quotient (AQ),[54] Transgender Congruence Scale (TCS),[55] and Gender Minority Stress and Resilience Measure (GMSRM),[56] which are given once a year after baseline. These questionnaires are employed to assess various aspects of TGD individuals' well-being. The WHOQOL-BREF, for instance, comprehensively evaluates QoL by examining physical health, psychological aspects, social relationships, and environmental factors.[57,58] The EDE-Q measures restraint, eating-, shape-, and weight concerns.[53] The AQ questionnaire is used to measure autistic traits by assessing five

domains including social skills, attention switching, attention to detail, communication, and imagination.[54] The TCS is included to measure appearance congruence and gender identity acceptance.[55] Lastly, the GMSRM is used to investigate gender-related discrimination, gender-related rejection, gender-related victimization, non affirmation of gender identity, internalized transphobia, negative expectations for future events, nondisclosure, community connectedness, and pride.[56]

The psychologic or psychiatric records include information on sexual orientation, age at sexual debut, past and current psychiatric diagnoses, previous psychological counselling, previous trauma, gender dysphoria in childhood, puberty or adolescence, age at first signs related to gender incongruence, puberty, awareness of the term "transgender", self-awareness of own transgenderism, reflection period concerning gender-affirming treatments and age at coming out. The gynaecologic and endocrinologic records include information on previously and currently prescribed GAHT, self-medication, anticonception, objective findings (height, weight, body mass index (BMI), blood pressure), results from blood tests (follicle stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone (TSH), haematocrit, creatinine, alanine transaminase (ALAT), alkaline phosphatase, free and total testosterone, oestradiol, prolactin, potassium, cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), sex hormone-binding globulin (SHBG)), chronic diseases, additional medication, egg- and sperm preservation and HPV vaccination.
Additionally, information from medical check-ups is included regarding the effects and possible side effects of GAHT. Lastly, information regarding approval or denial related to GAHT, mastectomy or breast construction, bottom-, laryngeal- and glottoplastic surgeries is included in the cohort as well as reasons for treatment discontinuation and dropout.

2.1.3 Data Management
Data are collected and managed using Research Electronic Data Capture (REDCap), an electronic data capture tool hosted at Aalborg University Hospital, Denmark.[59,60] REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data

downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources. Personal information is managed in compliance with the General Data Protection Regulation (GDPR) and the Danish Data Protection Act. [59,60]

2.1.4 Pilot Testing and Patient Involvement

Pilot testing was carried out by seven project staff members and six people unrelated to the CGI, who filled in and commented on the questionnaires to evaluate content and face validity. Subsequently, 16 patients from the CGI, Aalborg were involved in the development of the questionnaires by testing and providing feedback regarding the relevance, wording, and appropriateness of the questionnaires. They also assessed the burden and time required to complete the questionnaires, and their sense of inclusion in the questions. All feedback was considered in the further development of the questionnaires and resulted in changes related to phrasing, layout, grammar, and typing errors.

2.1.5 Ethics and Dissemination

Potential risks associated with this cohort centre around data collection and privacy concerns. It is acknowledged that the questionnaires contain personal and sensitive information which potentially leads to negative, uncomfortable, or distressing emotions among some patients. Hence, it is crucial to uphold the dignity, and autonomy of the patients. This is ensured by patients providing informed consent and maintaining the right to withdraw at any time. However, we consider that the benefits outweigh the minimal risks, as this cohort will generate new knowledge and understanding related to psychological and physiological aspects of gender identity and short- and long-term treatment effects. This comprehension is essential for enhancing the evidence base regarding gender-affirming care, which is an unmet need for this population. The cohort has been registered and approved by the North Jutland Region (no. F2024-012). Patients involved in this cohort can gain insight into the latest research by contacting the database administrator.

2.2 Original Study: Gender-affirming Hormone Therapy and Quality of Life

2.2.1 Study Participants

TGD patients from the TraCK were recruited for the original study between February 14 and May 6, 2024. Inclusion criteria for this study included informed consent provided by the patients, completion of the WHOQOL-BREF questionnaire,[52] and the ability to understand and read Danish due to the language of the questionnaires. Additional inclusion criteria specifically for the third research question were that patients must have undergone GAHT and received a blood test measuring oestradiol level for those AMAB and testosterone level for those AFAB, within approximately one month of completing the questionnaire. Another inclusion criterion was that patients in the GAHT group must have received GAHT for at least three months, whereas those in the control group must not have received any GAHT, either previously or within the last six months. Data from 360 patients were collected for this study.

2.2.2 Study Design

This study used a cross-sectional study design. Patients were divided into four groups based on their assigned sex at birth and whether they received GAHT. The four groups consisted of: patients AMAB who received GAHT, patients AMAB not receiving GAHT (control group), patients AFAB who received GAHT, and patients AFAB not receiving GAHT (control group).

2.2.3 Outcome Measures

Patients enrolled in this study completed the Danish version of the WHOQOL-BREF questionnaire, and their blood test results were collected from the TraCK.[61] The WHOQOL-BREF is a validated questionnaire consisting of 26 questions distributed across four domains: physical (D1), psychological (D2), social (D3), and environmental (D4) (with 7, 6, 3, and 8 questions, respectively).[42,52] The remaining two questions are related to general health, however, these are not included in this study. Each item was scored from 1 to 5, and the total score of each domain was transformed linearly to a 0-100 scale, where high scores indicate high QoL.[62] Missing data for a single question was managed by utilizing the average score from the other questions within the same domain to calculate the missing score.[63]

The Cronbach's coefficient alpha was calculated to be 0.85, 0.83, 0.67, and 0.80 for physical, psychological, social, and environmental factors, respectively.[52] The Spearman coefficient was

used to calculate the test-retest reliability for the Danish version of the WHOQOL-BREF with 0.86, 0.81, 0.84, and 0.84 for physical, psychological, social, and environmental factors, respectively.[52] The blood test included P-oestradiol from patients AMAB, and P-testosterone from patients AFAB and were utilized for subsequent analyses.

2.2.4 Data Analysis

Before conducting the statistical analysis, a statistical analysis plan (SAP) was developed to ensure the transparency and reproducibility of this study. Data was analysed using R (V. 2023.12.1+402). Based on the distribution, data were presented with means ($\pm$SD). To test for normality and homoscedasticity of the dependent variables Skewness and Kurtosis test and Levene's test were performed, respectively. Multivariate analysis of variance (MANOVA) tests were conducted to investigate the difference in the four QoL domains between patients AMAB receiving GAHT and controls, and patients AFAB receiving GAHT and controls. To investigate the difference in QoL domains between patients AMAB and patients AFAB receiving GAHT and controls MANOVA tests were performed. Two-sided t-tests were performed to investigate the difference in QoL for each domain both between treatment and control groups and between assigned sex at birth groups.

Furthermore, linear regression analyses were performed to investigate the relationship between hormone levels of P-oestradiol (pmol/L) (continuous) and P-testosterone (nmol/L) (continuous), and the four QoL domains (continuous) for patients AMAB and patients AFAB, respectively. Skewness and Kurtosis tests were used to test the normality of the residuals, and log transformation of the independent variables was performed. For each regression analysis, R^2 was calculated to investigate the amount of variation in the dependent variable that can be explained by the independent variable. Furthermore, regression coefficients and CI were calculated for each regression analysis.

To adjust for potential confounders (time in GAHT, age, GAS, and type of medication) a multivariable linear regression analysis for each QoL domain was performed. Time in GAHT was defined as time in months since the beginning of GAHT (continuous). GAS was defined as any gender-affirming surgery (yes/no). The type of medication was defined as either oral, transdermal patch, gel, or spray for patients AMAB, and injection and transdermal gel for patients AFAB (categorical).

3. Results

3.1 Results of the TraCK

1349 patients referred to the CGI received an invitation to participate in the TraCK. 490 patients (36%) answered the invitation and gave informed consent. However, one patient withdrew their consent, and 65 duplicates were identified in the database. Therefore, by May 6, 2024, 424 unique patients were included in the TraCK. Of these 424 patients, 52 patients (12%) did not complete all the questionnaires, leaving a total of 372 patients having completed all questionnaires. The distribution of assigned sex at birth and age, and whether they received GAHT can be seen in Table 1.

		AMAB	AFAB
Total n (%)		207 (100)	217 (100)
Age (Mean (SD))		32 (13)	27 (8)
GAHT n (%)	Yes	176 (85)	162 (75)
	No	31 (15)	55 (25)

Table 1. Overview of the 424 patients included in the TraCK. The number of patients assigned male at birth (AMAB) and patients assigned female at birth (AFAB) are illustrated, as well as age and whether they received gender-affirming hormone therapy (GAHT). SD: standard deviation. Percentages represent the portion of patients for each assigned sex at birth group.

3.2 Results of the Original Study

Data from 424 patients were collected for this study. Sixty-four patients were excluded from this study because they did not fulfil the inclusion criteria (45 patients due to incomplete responses to the WHOQOL-BREF questionnaire, 16 patients from the GAHT group due to receiving GAHT less than three months, and three patients from the control group due to receiving GAHT within the last six months), thus leaving 360 patients for further data analysis.

3.2.1 Demographics

Of the 360 patients, 169 patients were AMAB (143 receiving GAHT and 26 controls), and 191 patients were AFAB (141 receiving GAHT and 50 controls). Demographics regarding age, gender identity, education, ethnicity, and occupation are shown in Table 2.

	AMAB		AFAB	
Group	**GAHT**	**Control**	**GAHT**	**Control**
Total (n)	143	26	141	50
Age (Mean(SD))	33 (14)	28 (10)	28 (8)	25 (7)
	n (%)	n (%)	n (%)	n (%)
Gender Identity*				
Man	0 (0)	0 (0)	98 (70)	28 (56)
Woman	125 (87)	19 (73)	0 (0)	0 (0)
Predominantly man	1 (0.7)	0 (0)	33 (23)	10 (20)
Predominantly woman	24 (17)	3 (12)	0 (0)	0 (0)
Non-binary	19 (13)	6 (23)	35 (25)	17 (34)
Queer	16 (11)	5 (19)	28 (20)	6 (12)
Other gender identity[a]	15 (10)	9 (35)	25 (18)	10 (20)
Education				
Lower secondary school	14 (10)	3 (12)	15 (11)	6 (12)
10th grade	8 (6)	5 (19)	24 (17)	13 (26)
Vocational education	17 (12)	2 (8)	12 (9)	2 (4)
High school	46 (32)	9 (35)	42 (30)	19 (38)
Short-cycle higher education	9 (6)	1 (4)	7 (5)	2 (4)
Medium-cycle higher education	24 (17)	4 (15)	25 (18)	3 (6)
Long-cycle higher education	19 (13)	2 (8)	13 (9)	2 (4)
Other[b]	6 (4)	0 (0)	3 (2)	3 (6)
Ethnicity				
Danish	123 (86)	20 (77)	112 (79)	39 (78)
Other[c]	20 (14)	6 (23)	29 (21)	11 (22)
Occupation				
Employed	47 (33)	6 (23)	43 (30)	7 (14)
Unemployed	6 (4)	2 (8)	8 (6)	1 (2)
Enrolled in education	33 (23)	11 (42)	41 (29)	22 (44)
Financial assistance	20 (14)	1 (4)	23 (16)	7 (14)
Early retirement pension	14 (10)	1 (4)	9 (6)	4 (8)
Other[d]	23 (16)	5 (19)	17 (12)	8 (16)

Table 2. Demographics of the 360 patients included in the original study. a: both man and woman, neither man nor woman, agender, gender-fluid, don't know, unsure, b: not completed lower secondary school, specially planned youth education (STU), c: Faroese, Polish, Indian, half Greek, Icelander, Slovaks, Greenlander, German, half Moroccan, Norwegian, South African, English, French, Venezuelan, American, Roman, Italian, Spanish, Thai, half Iranian, Russian, Singaporean, Swiss, Korean, half Turkish, Finnish, Bosnian, Chinese, Australian, Kurdish, Dutch, no answer, d: Flex job, state pension, sickness benefits, living of own savings, supported by a partner, supported by family, supported by a friend. SD: standard deviation. Percentages represent the portion of patients in each group. *n may exceed the total number of patients in each group as it is possible to have multiple gender identities.

3.2.2 Relationship between GAHT and QoL

A statistically significant difference in mean QoL scores between the GAHT- and the control group for patients AMAB was found (p = 0.005) (Figure 1a). Furthermore, a statistically significantly higher mean QoL score of D2 for the GAHT group (51.4) compared to the control group (36.9) was found for patients AMAB (p = 0.003). However, no statistically significant difference in mean QoL scores for D1, D3, and D4 between the GAHT- and the control group was found for patients AMAB (p = 0.699; p = 0.552; p = 0.063, respectively) (Appendix 7.1). For patients AFAB a statistically significant difference in mean QoL scores between the GAHT- and the control group was also found (p = 0.021) (Figure 1b). A statistically significantly higher mean score of D2 for the GAHT group (53.9) compared to the control group (44.3) was also found for patients AFAB (p = 0.004). No statistically significant difference in mean QoL scores of D1, D3 and D4 was found for patients AFAB (p = 0.065, p = 0.949; p = 0.099, respectively) (Appendix 7.1).

3.2.3 Relationship between Assigned Sex at Birth and QoL

There was a significant difference in mean QoL scores between patients AMAB and patients AFAB in the GAHT group (p = 0.010) (Figure 1c). Furthermore, the mean QoL score of D3 for those receiving GAHT was significantly higher for patients AFAB (65.4) than patients AMAB (57.5) (p = 0.001). However, there was no significant difference in mean QoL scores of D1, D2, and D4 for those receiving GAHT between patients AFAB and patients AMAB (p = 0.126; p = 0.310; p = 0.053, respectively) (Appendix 7.2). For patients in the control group, a significant difference in mean QoL scores between patients AMAB and patients AFAB was found (p = 0.042) (Figure 1d). Nevertheless, no significant difference was found in the control group regarding all four QoL domain scores between patients AFAB and patients AMAB, (p = 0.779; p = 0.146; p = 0.059; p = 0.125, respectively) (Appendix 7.2).
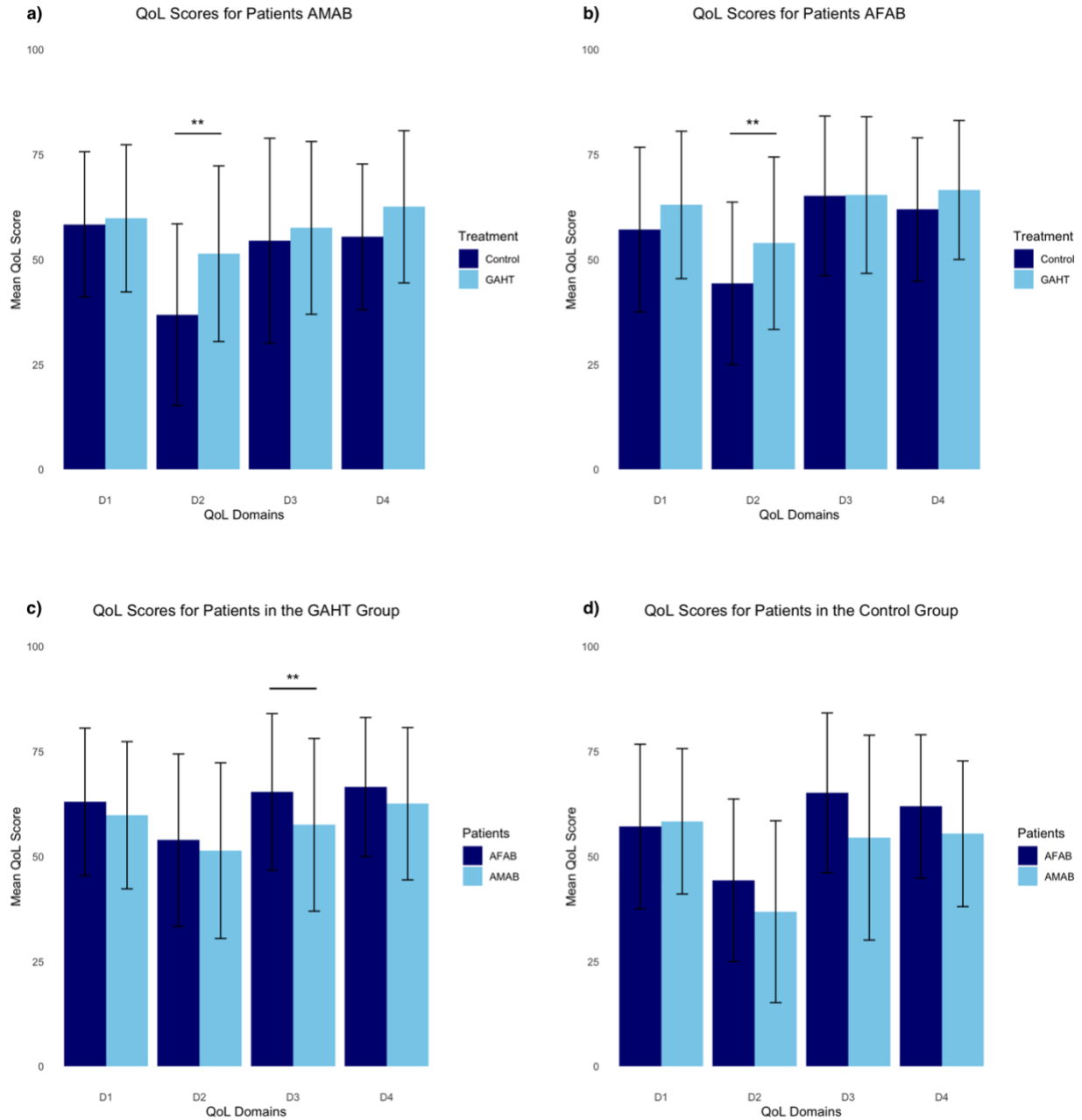
*Figure 1. Bar charts illustrating mean Quality of Life (QoL) scores on the y-axis for each QoL domain (D1: physical; D2: psychological; D3: social; D4: environmental) on the x-axis. a) QoL mean scores for gender-affirming hormone therapy (GAHT) and control groups for patients assigned male at birth (AMAB) (n = 143; n = 26, respectively). b) QoL mean scores for GAHT and control groups for patients assigned female at birth (AFAB) (n = 141; n = 50, respectively). c) QoL mean scores for patients AMAB and patients AFAB in the GAHT group (n = 143; n = 141, respectively). d) QoL mean scores for patients AMAB and patients AFAB in the control group (n = 26; n = 50, respectively). Standard deviations are illustrated as error bars. Significant differences in each domain are marked with ** indicating a significance level of less than 0.01.*

3.2.4 Relationship between Oestradiol Levels and QoL

71 patients AMAB were included in this analysis. Regression coefficients, CI, and R^2-values are shown in Table 3. Figure 2 illustrates the linear regression plot representing the relationship between oestradiol levels and the four QoL domain scores.

QoL Domain	α	β	Lower CI	Upper CI	R^2
D1	59.35	0.10	-10.88	11.09	-0.014
D2	51.10	0.49	-13.50	14.47	-0.014
D3	65.66	-2.45	-15.57	10.68	-0.012
D4	60.02	0.45	-12.48	13.38	-0.014

Table 3. Relationship between oestradiol levels and quality of life (QoL) domain scores for patients assigned male at birth. Regression coefficients, lower and upper confidence intervals (CI), and R^2 for each QoL domain (D1: physical; D2: psychological; D3: social; D4: environmental) are illustrated. n = 71.
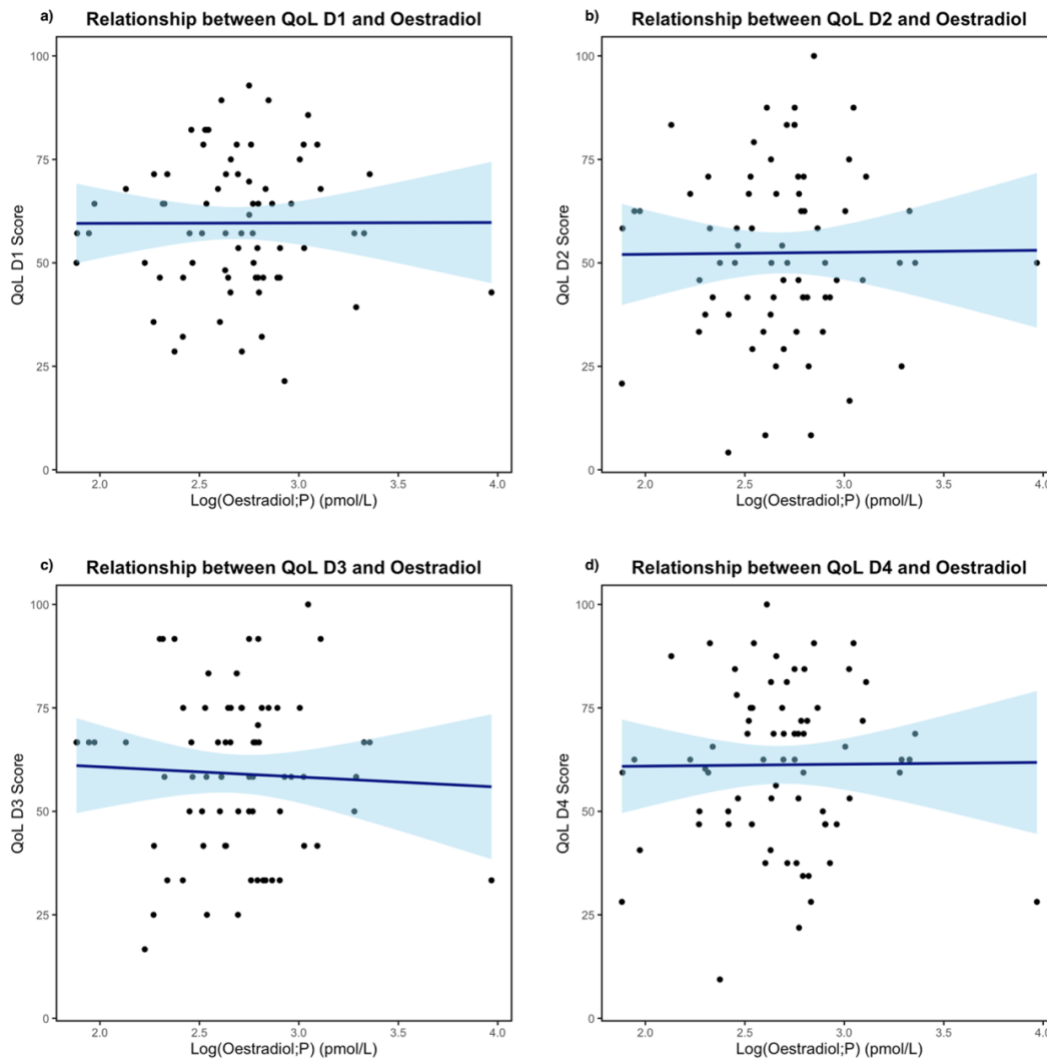

Figure 2. Relationship between oestradiol levels and the four quality of life (QoL) domain scores for patients assigned male at birth, a) D1: physical, b) D2: psychological, c) D3: social, d) D4: environmental. The y-axes represent the QoL domain scores and the x-axes represent log(Oestradiol; P) in pmol/L. Confidence intervals are illustrated with a light blue colour. n = 71.

3.2.5 Relationship between Testosterone Levels and QoL

69 patients AFAB were included in this analysis. Regression coefficients, CI, and R^2-values are illustrated in Table 4. Figure 3 illustrates the linear regression plot representing the relationship between testosterone levels and the four QoL domain scores.

QoL Domain	a	b	Lower CI	Upper CI	R^2
D1	49.56	9.93	-10.76	30.62	-0.001
D2	45.85	7.03	-15.50	29.57	-0.009
D3	56.41	7.73	-13.25	28.71	-0.007
D4	56.83	8.71	-9.89	27.32	-0.002

Table 4. Relationship between testosterone levels and quality of life (QoL) domain scores for patients assigned female at birth. Regression coefficients, lower and upper confidence intervals (CI), and R^2 for each QoL domain (D1: physical; D2: psychological; D3: social; D4: environmental) are illustrated. n = 69.
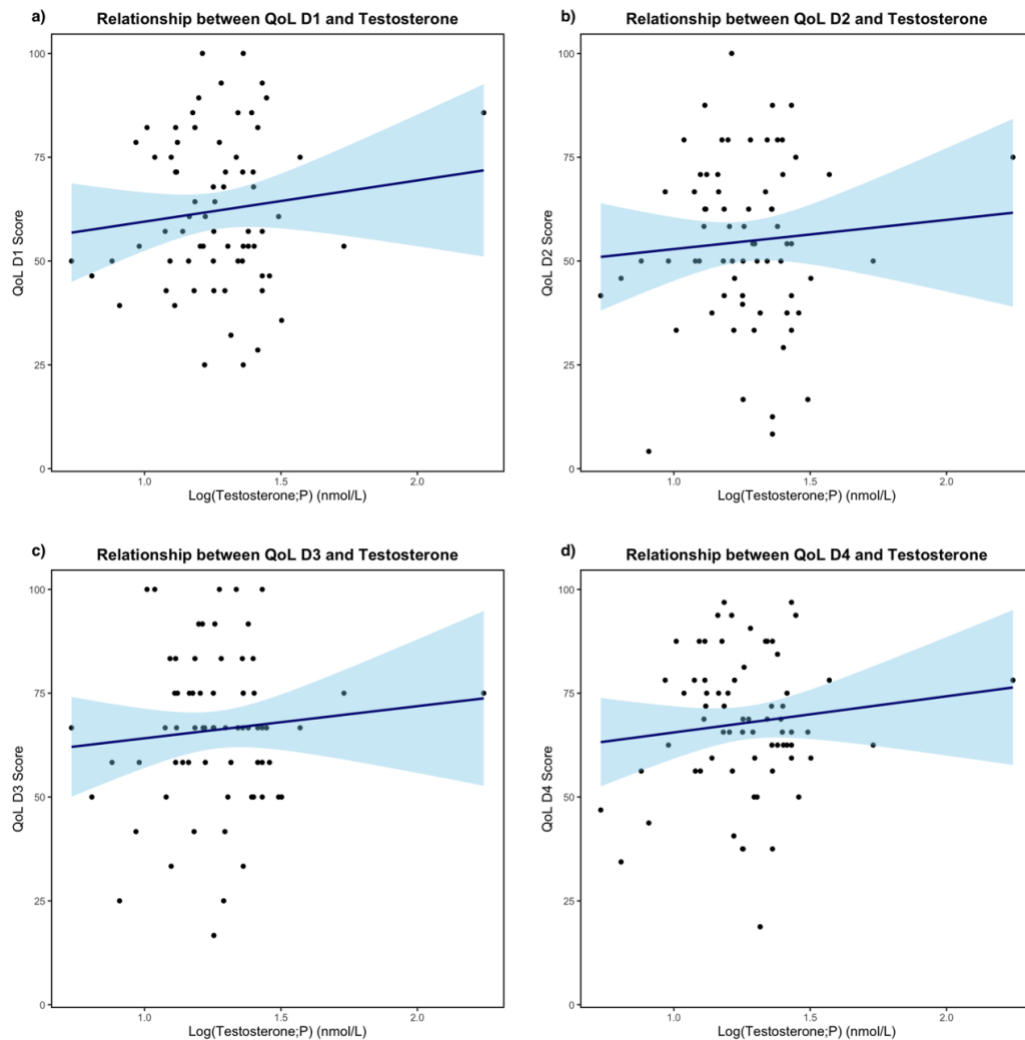

Figure 3. Relationship between testosterone levels and the four quality of life (QoL) domain scores for patients assigned female at birth, a) D1: physical, b) D2: psychological, c) D3: social, d) D4: environmental. The y-axes represent the QoL domain scores and the x-axes represent log(Testosterone; P) in nmol/L. Confidence intervals are illustrated with a light blue colour. n = 69.

3.2.6 Confounder adjusted Relationship between GAHT and QoL

The relationship between GAHT and QoL for patients AMAB and patients AFAB in unadjusted and adjusted analyses are presented in Table 5 and Table 6, respectively.

		Unadjusted			Adjusted		
QoL Domain		Unadjusted coefficients	Lower CI	Upper CI	Adjusted coefficients	Lower CI	Upper CI
D1	GAHT	1.13	-6.22	8.47	21.97	-274.89	318.83
D2	GAHT	14.53	5.63	23.43	19.68	-318.34	357.69
D3	GAHT	3.05	-5.90	12.00	18.86	-330.72	368.44
D4	GAHT	7.25	-0.38	14.88	35.30	-269.94	340.54

Table 5. Relationship between gender-affirming hormone therapy (GAHT) and the four quality of life (QoL) domains (D1: physical; D2: psychological; D3: social; D4: environmental) for patients assigned male at birth. The adjusted model is adjusted for time in GAHT, age, gender-affirming surgery, and type of medication. CI: confidence interval.

		Unadjusted			Adjusted		
QoL Domain		Unadjusted coefficients	Lower CI	Upper CI	Adjusted coefficients	Lower CI	Upper CI
D1	GAHT	6.46	0.56	12.36	-91.50	-224.81	41.80
D2	GAHT	10.19	3.60	16.79	-74.96	-222.16	72.25
D3	GAHT	0.40	-5.75	6.55	-112.94	-252.67	26.79
D4	GAHT	5.10	-0.35	10.55	5.87	-119.01	130.74

Table 6. Relationship between gender-affirming hormone therapy (GAHT) and the four quality of life (QoL) domains (D1: physical; D2: psychological; D3: social; D4: environmental) for patients assigned female at birth. The adjusted model is adjusted for time in GAHT, age, gender-affirming surgery, and type of medication. CI: confidence interval.

4. Discussion

4.1 The Development of the TraCK

It was possible to develop a comprehensive database using a web-based platform for TGD individuals with a fair response rate of 36%.

4.1.1 Strengths and Limitations of the Development of the TraCK

The TraCK provides a systematic overview of TGD individuals and establishes a foundation for future research. With the TraCK, it is possible to monitor short- and long-term treatment effects on physical and mental health, as it enables follow-up of patients. The TraCK is a comprehensive database, which includes diverse questionnaires that examine different aspects of TGD individuals' well-being, alongside information extracted from psychological, psychiatric, gynaecological, and endocrinological records. Furthermore, the TraCK was developed in a multidisciplinary collaboration, providing diverse perspectives on its content and structure. The questionnaires included in the TraCK have been validated by project staff members, people unrelated to the CGI, and patients from the CGI, hence evaluating face and content validity. Nevertheless, there is a risk of selection bias in the TraCK, as only patients referred to the CGI are included, and patients decide whether they want to participate. Additionally, some TGD individuals seeking treatment may be hesitant to provide personal information because of fear of rejection. As many TGD individuals face a variety of mental health problems and other challenges in their daily lives, it can be discussed if only those with surplus energy have answered the questionnaires and if the cohort is representative of the TGD population.

4.2 The Original Study

Overall, our study found a statistically significant difference in QoL between patients receiving GAHT and controls for both patients AMAB and patients AFAB. Specifically, statistically significantly higher scores in D2 were observed for the GAHT group for both patient groups. Furthermore, a statistically significant difference between patients AMAB and patients AFAB in the GAHT group was found, with patients AFAB showing higher scores in D3. Our study found no statistically significant relationship between levels of oestrogen and testosterone and QoL domain scores for patients AMAB and patients AFAB, respectively.

4.2.1 GAHT and QoL

The findings from our study are consistent with the overall findings from a systematic review by Van Leerdam et al. 2023 which found that GAHT improves the QoL of TGD individuals, even though the results were mixed.[64] However, a systematic review by Doyle et al. in 2023 revealed inconclusive evidence concerning QoL following GAHT for both transgender women (TW) and transgender men (TM), though there were indications of potential improvements in psychosocial functioning.[24] It is important to consider that most studies included in the review by Van Leerdam et al. provide low to moderate levels of evidence, and the risk of bias was highly variable in the studies included in the review by Doyle et al.[24,64] Notably, studies reporting no difference or a decline in QoL after GAHT included individuals who used GAHT without a medical prescription, potentially leading to uncontrolled usage, which is in contrast to our study.[24,64] This may suggest that barriers to healthcare and discrimination still persist among TGD individuals in certain countries, which may affect their QoL.[64]

Consistent with our study, studies by Gómez-Gil et al. and Manieri et al. reported improvements in QoL assessed by the WHOQOL-BREF and WHOQOL-100 following GAHT, respectively.[65,66] The study by Gómez-Gill et al. found a significant improvement in the psychological and social QoL domains for transgender individuals following GAHT compared to those who did not receive GAHT, which is consistent with the findings from the psychological domain in our study.[65] Compared to our study, the prospective cohort study by Manieri et al., found a significant improvement in the general QoL only among TW and not for TM after initiating GAHT.[66] This could be due to the difference in study design, and because they included a smaller number of participants. Further, the study by Manieri et al. had a smaller sample size for TM than for TW (TM: n=27; TW: n=56), which could be a reason why they only found an improvement in general QoL for TW.[66]

Comparable to the study by Gómez-Gill et al., a study by Gorin-Lazard et al. in 2012 also found a significant improvement in the social and psychological QoL dimension for individuals AMAB and individuals AFAB receiving GAHT, however, they did not find a difference in QoL between individuals AMAB and AFAB following GAHT.[67] This finding is in contrast to our study, where a significantly higher QoL score in D3 was found for patients AFAB compared to patients AMAB receiving GAHT. An explanation for this could be the larger sample size of our study

compared to the sample size of Gorin-Lazard et al. (AMAB: n=31; AFAB: n=30).[67] The significant difference found in our study could be explained by the faster onset of physical changes following masculinizing GAHT compared to feminizing GAHT. For example, patients AFAB experience a change in voice three months after initiating GAHT, whereas a change in voice is not possible for patients AMAB if GAHT is initiated after puberty, which can impact social relations.[68] In addition, patients AFAB get faster access to top surgery, min. 6 months after initiating GAHT, compared to 12 to 24 months for patients AMAB.[69] Altogether, these factors can influence body image which may affect the way individuals AMAB and individuals AFAB respond to social settings. Moreover, the difference in the psychological domain between individuals receiving GAHT and those who do not, found in our study, as well as in the studies by Gomez-Gill et al. and Gorin-Lazard et al., might be due to the physical changes contributing to enhanced self-esteem and reduced levels of anxiety and depression.[6,65,67]

Nevertheless, some studies did not find a relationship between QoL and GAHT.[34,70,71] A study by Simbar et al. found no difference in QoL following GAHT for both individuals AMAB and individuals AFAB. In contrast to our study, the study by Simbar et al. only assessed an overall score for the WHOQOL-BREF, possibly leading to the oversight of any potential differences in specific domain scores, which could have influenced the results.[70] Compared to Simbar et al. studies by Foster Skewis et al. and Filipov et al. used QoL scores for each domain.[34,70,71] However, the study by Filipov et al. still did not find a difference in QoL following GAHT for individuals AFAB compared to those who did not receive GAHT which could be due to the small sample size of this study.[71] In addition, the study by Foster Skewis et al. did not find a difference in QoL for individuals AMAB after initiating GAHT.[34] Notably, the study by Foster Skewis et al. differs from our study and the other two studies in terms of study design and the QoL assessment tool utilized, as the study by Foster Skewis et al. is a prospective cohort study and uses the RAND SF-36 questionnaire.[34,70,71]

4.2.2 Sex Hormone Levels and QoL

Our study did not find a linear relationship between oestradiol levels and QoL, which could be due to multiple effects of oestradiol. On the one hand, feminizing GAHT facilitates the transitioning process by inducing physical changes, which may enhance certain aspects of QoL.[22] On the other hand, the negative effects of oestradiol on the mental well-being of TGD individuals could also influence the QoL of patients AMAB.[37] Although there is a lack of knowledge regarding the effects of oestradiol on QoL and mental health of individuals AMAB, the effect of hormonal contraceptives is widely investigated in cisgender women.[72,73] Multiple studies have found an association between the use of hormonal contraceptives and depression.[72,73] A systematic review has also found that hormonal contraceptives can lead to structural and functional changes in brain areas involved in affective and cognitive processing, which could be an explanation for why depression is common among women using hormonal contraceptives.[74]

Even though, our study did not find a relationship between testosterone and QoL, other studies found an improvement in mental well-being after the administration of testosterone.[37,75,76] A study by Giltay et al., demonstrated that masculinizing GAHT had a beneficial impact on different mental factors.[37] Similarly, these findings correspond with research on cisgender women, indicating that administering low doses of testosterone to cisgender women, as opposed to a placebo, leads to an improvement in depression and anxiety symptoms.[75,76] However, another study by Rohr et al. reported that high testosterone levels in women can have the opposite effect, thus administrating too much testosterone can negatively affect mood and lead to major depression disorders.[77] This could be a part of the explanation for why we did not find a significant linear relationship between testosterone levels and QoL.

4.2.3 Strengths and Limitations of the Original Study

Our study utilized a combination of subjective and objective data from the TraCK, which included self-reported responses from the WHOQOL-BREF questionnaire and blood tests of oestradiol and testosterone. This comprehensive approach ensured that the study had access to high-quality data from a diverse cohort of TGD patients encompassing individuals with diverse gender identities and undergoing various gender-affirming treatments.

By investigating the difference in QoL between TGD patients receiving GAHT and controls, our study contributes new insights into the knowledge gap of existing evidence within this field. Additionally, our study also compared QoL between patients AMAB and patients AFAB, which contributes to an understanding of gender-specific differences in QoL. Furthermore, this study is the first to explore the relationship between sex hormone levels and QoL among TGD individuals, thus providing valuable insights into the relationship between physiological measurements and QoL. To measure QoL four domain scores were calculated and analysed instead of a total QoL score, which provided a more comprehensive understanding of different aspects of QoL. As various factors can influence QoL, possible confounders such as time in GAHT, age, GAS, and type of medication were included in the analysis, however, the confounder-adjusted analyses yielded comparable results to the unadjusted analysis, except for the association between GAHT and QoL D1-3 for patients AFAB.

However, our study also has some limitations. We used a cross-sectional study design dividing the relatively large sample of 360 TGD patients into four smaller subgroups. These small subgroups set a limitation for the numbers of sub- and confounder-adjusted analyses. Because the WHOQOL-BREF relies on subjective interpretation of the questions, the internal validity of the questionnaire might have been affected, as patients could have interpreted certain questions differently. Furthermore, this study has not taken previous or current psychiatric diagnoses e.g. depression and anxiety into account, which would have been a major advantage as it is known that mental factors can influence QoL and thereby the results of our study. Another limitation was the presence of missing data in questionnaire items for some patients. However, this was handled in the analysis by imputation. Regarding the blood tests of sex hormones, a limitation was the inability to obtain these samples precisely at the same time as the completion of the questionnaire responses. Consequently, there was a maximum time difference of one month between the two measurements. In addition, both the time of day for blood sampling and the time between administering GAHT and the blood sampling could be a limitation of this study, as levels of sex hormones can change throughout the day and rise significantly after the administration of GAHT.

4.3 Future Perspectives

For future studies, it would be beneficial to follow TGD individuals initiating GAHT over time and investigate their QoL through prospective cohort studies that consider interpersonal variations. This will be possible using data from the TraCK in the future when follow-up data become available. It would be interesting to investigate sex hormone levels and QoL both measured on the same day and to include a larger sample size. This study found a difference in QoL between assigned sex at birth groups, highlighting the importance of distinguishing between individuals AMAB and individuals AFAB in future studies to gain a more comprehensive understanding of the well-being of TGD individuals. This difference between assigned sex at birth groups is also an essential aspect for healthcare providers to recognize.

5. Conclusion

In conclusion, it was possible to establish a comprehensive database of TGD patients. In addition, this study found that QoL for patients receiving GAHT was statistically significantly higher compared to controls for both patients AMAB and patients AFAB. A statistically significantly higher QoL score was only found for the psychological domain for patients receiving GAHT compared to controls for both patient groups. Additionally, a statistically significantly higher QoL was found for patients AFAB compared to patients AMAB. However, only a statistically significantly higher QoL score was found in the social domain for patients AFAB compared to patients AMAB receiving GAHT. Furthermore, no linear relationship was found between sex hormone levels and QoL. With these findings, this study provides insights into how GAHT impacts the QoL of TGD individuals, highlighting the advantages of offering GAHT to this population. All of this contributes new knowledge and can thereby create more attention for evidence-based treatment of TGD individuals, which can significantly improve their well-being and healthcare outcomes.

6. Bibliography

1. Rajkovic A, Cirino AL, Berro T, Koeller DR, Zayhowski K. Transgender and gender-diverse (TGD) individuals' perspectives on research seeking genetic variants associated with TGD identities: a qualitative study. J Community Genet. 2022;13:31–48.

2. Frisch M, Aalborg Universitet, Statens Serum Institut, Projekt SEXUS, Statens Serum Institut (Afdeling for Epidemiologisk Forskning), Aalborg Universitet (Sexologisk Forskningscenter KI. Sex i Danmark : nøgletal fra Projekt SEXUS 2017-2018. Statens Serum Institut; 2019.

3. Herman JL, Flores AR, O'Neill KK. How Many Adults and Youth Identify as Transgender in the United States? [Internet]. 2022 Jun [cited 2024 Jan 10]. Available from: https://williamsinstitute.law.ucla.edu/publications/trans-adults-united-states/

4. Arcelus J, Bouman WP, Van Den Noortgate W, Claes L, Witcomb G, Fernandez-Aranda F. Systematic Review and Meta-Analysis of Prevalence Studies in Transsexualism. European Psychiatry. 2015;30:807–15.

5. Van Caenegem E, Wierckx K, Elaut E, Buysse A, Dewaele A, Van Nieuwerburgh F, et al. Prevalence of Gender Nonconformity in Flanders, Belgium. Arch Sex Behav. 2015;44:1281–7.

6. Heylens G, Elaut E, Kreukels BPC, Paap MCS, Cerwenka S, Richter-Appelt H, et al. Psychiatric characteristics in transsexual individuals: multicentre study in four European countries. British Journal of Psychiatry. 2014;204:151–6.

7. Drabish K, Theeke LA. Health Impact of Stigma, Discrimination, Prejudice, and Bias Experienced by Transgender People: A Systematic Review of Quantitative Studies. Issues Ment Health Nurs. 2022;43:111–8.

8. Wilson LC, Newins AR, Kassing F, Casanova T. Gender Minority Stress and Resilience Measure: A Meta-Analysis of the Associations with Mental Health in Transgender and Gender Diverse Individuals. Trauma Violence Abuse. 2023;

9. Warrier V, Greenberg DM, Weir E, Buckingham C, Smith P, Lai MC, et al. Elevated rates of autism, other neurodevelopmental and psychiatric diagnoses, and autistic traits in transgender and gender-diverse individuals. Nat Commun. 2020;11:3959.

10. Rasmussen SM, Dalgaard MK, Roloff M, Pinholt M, Skrubbeltrang C, Clausen L, et al. Eating disorder symptomatology among transgender individuals: a systematic review and meta-analysis. J Eat Disord. 2023;11:84.

11. McGuire JK, Doty JL, Catalpa JM, Ola C. Body image in transgender young people: Findings from a qualitative, community based study. Body Image. 2016;18:96–107.

12. Leinung MC, Joseph J. Changing Demographics in Transgender Individuals Seeking Hormonal Therapy: Are Trans Women More Common Than Trans Men? Transgend

Health [Internet]. 2020 [cited 2024 Jan 22];5:241–5. Available from:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7906237/#B4

13. Pop ML, Højgaard AD, Bruun NH, Giami A. An investigation of self-medication among
gender-diverse individuals: comparison between a clinical sample and a survey sample. J
Sex Med. 2022;19:S62–3.

14. Mepham N, Bouman WP, Arcelus J, Hayter M, Wylie KR. People with Gender Dysphoria
Who Self-Prescribe Cross-Sex Hormones: Prevalence, Sources, and Side Effects
Knowledge. J Sex Med. 2014;11:2995–3001.

15. Goulding R, Goodwin J, O'Donovan A, Saab MM. Transgender and gender diverse
youths' experiences of healthcare: A systematic review of qualitative studies. Journal of
Child Health Care. 2023;

16. Wright T, Nicholls EJ, Rodger AJ, Burns FM, Weatherburn P, Pebody R, et al. Accessing
and utilising gender-affirming healthcare in England and Wales: trans and non-binary
people's accounts of navigating gender identity clinics. BMC Health Serv Res.
2021;21:609.

17. Karasic DH, Fraser L. Multidisciplinary Care and the Standards of Care for Transgender
and Gender Nonconforming Individuals. Clin Plast Surg. 2018;45:295–9.

18. Ross MB, Jahouh H, Mullender MG, Kreukels BPC, van de Grift TC. Voices from a
Multidisciplinary Healthcare Center: Understanding Barriers in Gender-Affirming Care—
A Qualitative Exploration. Int J Environ Res Public Health. 2023;20:6367.

19. World Health Organization. Gender incongruence and transgender health in the ICD
[Internet]. [cited 2024 Feb 14]. Available from:
https://www.who.int/standards/classifications/frequently-asked-questions/gender-
incongruence-and-transgender-health-in-the-icd

20. Oates J, Södersten M, Quinn S, Nygren U, Dacakis G, Kelly V, et al. Gender-Affirming
Voice Training for Trans Women: Effectiveness of Training on Patient-Reported
Outcomes and Listener Perceptions of Voice. Journal of Speech, Language, and Hearing
Research. 2023;66:4206–35.

21. Ginsberg BA, Calderon M, Seminara NM, Day D. A potential role for the dermatologist in
the physical transformation of transgender people: A survey of attitudes and practices
within the transgender community. J Am Acad Dermatol. 2016;74:303–8.

22. T'Sjoen G, Arcelus J, Gooren L, Klink DT, Tangpricha V. Endocrinology of Transgender
Medicine. Endocr Rev [Internet]. 2019 [cited 2024 Jan 23];40:97–117. Available from:
https://pubmed.ncbi.nlm.nih.gov/30307546/

23. Nguyen HB, Chavez AM, Lipner E, Hantsoo L, Kornfield SL, Davies RD, et al. Gender-
Affirming Hormone Use in Transgender Individuals: Impact on Behavioral Health and
Cognition. Curr Psychiatry Rep. 2018;20:110.

24.   Doyle DM, Lewis TOG, Barreto M. A systematic review of psychosocial functioning changes after gender-affirming hormone therapy among transgender people. Nat Hum Behav. 2023;7:1320–31.

25.   T'Sjoen G, Arcelus J, De Vries ALC, Fisher AD, Nieder TO, Özer M, et al. European Society for Sexual Medicine Position Statement "Assessment and Hormonal Management in Adolescent and Adult Trans People, with Attention for Sexual Function and Satisfaction." J Sex Med. 2020;17:570–84.

26.   Glintborg D, T'Sjoen G, Ravn P, Andersen MS. MANAGEMENT OF ENDOCRINE DISEASE: Optimal feminizing hormone treatment in transgender people. Eur J Endocrinol. 2021;185:R49–63.

27.   Glintborg D, Rubin KH, Kristensen SB, Lidegaard Ø, T'Sjoen G, Hilden M, et al. Gender affirming hormonal treatment in Danish transgender persons: A nationwide register-based study. Andrology. 2022;10:885–93.

28.   Tangpricha V, den Heijer M. Oestrogen and anti-androgen therapy for transgender women. Lancet Diabetes Endocrinol. 2017;5:291–300.

29.   Hojbjerg JA, Saini SL, Hvas AM, Hojgaard AD. Current Treatment Regimens for Transfeminine Individuals in the Nordic Countries. J Sex Med. 2021;18:656–63.

30.   Hembree WC, Cohen-Kettenis PT, Gooren L, Hannema SE, Meyer WJ, Murad MH, et al. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society* Clinical Practice Guideline. J Clin Endocrinol Metab. 2017;102:3869–903.

31.   Defreyne J, Vander Stichele C, Iwamoto SJ, T'Sjoen G. Gender-affirming hormonal therapy for transgender and gender-diverse people—A narrative review. Best Pract Res Clin Obstet Gynaecol. 2023;86:102296.

32.   Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, et al. Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People, Version 7. International Journal of Transgenderism. 2012;13:165–232.

33.   Santos RB, Lemos C, Saraiva M. Gender-Affirming Hormone Therapy: Physical and Sociopsychological Effects, Impact and Satisfaction. Cureus [Internet]. 2023 [cited 2023 Sep 14]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10118284/#:~:text=Gender%2Daffirming%20hormone%20therapy%20(GAHT)%20is%20not%20exempt%20from,therapy%20%5B%2C7%5D

34.   Foster Skewis L, Bretherton I, Leemaqz SY, Zajac JD, Cheung AS. Short-Term Effects of Gender-Affirming Hormone Therapy on Dysphoria and Quality of Life in Transgender Individuals: A Prospective Controlled Study. Front Endocrinol (Lausanne) [Internet]. 2021 [cited 2023 Sep 14];12. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8358932/

35.   Hilden M, Glintborg D, Andersen MS, Kyster N, Rasmussen SC, Tolstrup A, et al. Gender incongruence in Denmark, a quantitative assessment. Acta Obstet Gynecol Scand. 2021;100:1800–5.

36.   Gooren LJ, Giltay EJ, Bunck MC. Long-Term Treatment of Transsexuals with Cross-Sex Hormones: Extensive Personal Experience. J Clin Endocrinol Metab. 2008;93:19–25.

37.   Giltay EJ, Bunck MC, Gooren LJ, Zitman FG, Diamant M, Teerlink T. Effects of Sex Steroids on the Neurotransmitter-Specific Aromatic Amino Acids Phenylalanine, Tyrosine, and Tryptophan in Transsexual Subjects. Neuroendocrinology [Internet]. 2008 [cited 2024 Jan 23];88:103–10. Available from: https://karger.com/nen/article/88/2/103/226127/Effects-of-Sex-Steroids-on-the-Neurotransmitter#:~:text=Through%20this%20mechanism%2C%20sex%20steroids,delet erious%2C%20and%20testosterone%20beneficial%20effects.

38.   Barth C, Villringer A, Sacher J. Sex hormones affect neurotransmitters and shape the adult female brain during hormonal transition periods. Front Neurosci [Internet]. 2015 [cited 2024 Jan 23];9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4335177/

39.   Salehpoor G, Rezaei S, Hosseininezhad M. Quality of life in multiple sclerosis (MS) and role of fatigue, depression, anxiety, and stress: A bicenter study from north of Iran. Iran J Nurs Midwifery Res. 2014;19:593–9.

40.   Rieu I, Houeto JL, Pereira B, De Chazeron I, Bichon A, Chéreau I, et al. Impact of Mood and Behavioral Disorders on Quality of Life in Parkinson's disease. J Parkinsons Dis. 2016;6:267–77.

41.   Zitzmann M. Testosterone, mood, behaviour and quality of life. Andrology. 2020;8:1598–605.

42.   Vahedi S. World Health Organization Quality-of-Life Scale (WHOQOL-BREF): Analyses of Their Item Response Theory Properties Based on the Graded Responses Model. Iran J Psychiatry. 2010;5:140–53.

43.   Jones BA, Pierre Bouman W, Haycraft E, Arcelus J. Mental health and quality of life in non-binary transgender adults: a case control study. International Journal of Transgenderism. 2019;20:251–62.

44.   Magano S, Maleitas M, Santos G. Quality of life in trangender people - a systematic review. J Sex Med. 2022;19:S61.

45.   Engel L, Majmudar I, Mihalopoulos C, Tollit MA, Pang KC. Assessment of Quality of Life of Transgender and Gender-Diverse Children and Adolescents in Melbourne, Australia, 2017-2020. JAMA Netw Open. 2023;6:e2254292.

46.   Baker KE, Wilson LM, Sharma R, Dukhanin V, McArthur K, Robinson KA. Hormone Therapy, Mental Health, and Quality of Life Among Transgender People: A Systematic

Review. J Endocr Soc [Internet]. 2021 [cited 2024 Jan 23];5. Available from: https://pubmed.ncbi.nlm.nih.gov/33644622/

47. Rowniak S, Bolt L, Sharifi C. Effect of cross-sex hormones on the quality of life, depression and anxiety of transgender individuals: a quantitative systematic review. JBI Database System Rev Implement Rep [Internet]. 2019 [cited 2024 Jan 23];17:1826–54. Available from: https://pubmed.ncbi.nlm.nih.gov/31021971/

48. Meyer G, Boczek U, Bojunga J. Hormonal Gender Reassignment Treatment for Gender Dysphoria. Dtsch Arztebl Int [Internet]. 2020 [cited 2024 Jan 23]; Available from: https://pubmed.ncbi.nlm.nih.gov/33559593/

49. Silva ED, Fighera TM, Allgayer RM, Lobato MIR, Spritzer PM. Physical and Sociodemographic Features Associated With Quality of Life Among Transgender Women and Men Using Gender-Affirming Hormone Therapy. Front Psychiatry [Internet]. 2021 [cited 2024 Jan 23];12. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8350045/#B9

50. Van Goozen SHM, Cohen-Kettenis PT, Gooren LJG, Frijda NH, Van De Poll NE. Gender differences in behaviour: Activating effects of cross-sex hormones. Psychoneuroendocrinology. 1995;20:343–63.

51. Gorin-Lazard A, Baumstarck K, Boyer L, Maquigneau A, Penochet JC, Pringuey D, et al. Hormonal Therapy Is Associated With Better Self-esteem, Mood, and Quality of Life in Transsexuals. Journal of Nervous & Mental Disease [Internet]. 2013 [cited 2024 Jan 23];201:996–1000. Available from: https://pubmed.ncbi.nlm.nih.gov/24177489/

52. Bech VNP. The WHO Quality of Life (WHOQOL) Questionnaire: Danish validation study. Nord J Psychiatry. 2001;55:229–35.

53. Lichtenstein MB, Haastrup L, Johansen KK, Bindzus JB, Larsen PV, Støving RK, et al. Validation of the Eating Disorder Examination Questionnaire in Danish Eating Disorder Patients and Athletes. J Clin Med [Internet]. 2021 [cited 2024 Jan 10];10:3976. Available from: https://pubmed.ncbi.nlm.nih.gov/34501422/

54. Lundqvist LO, Lindner H. Is the Autism-Spectrum Quotient a Valid Measure of Traits Associated with the Autism Spectrum? A Rasch Validation in Adults with and Without Autism Spectrum Disorders. J Autism Dev Disord. 2017;47:2080–91.

55. Kozee HB, Tylka TL, Bauerband LA. Measuring Transgender Individuals' Comfort With Gender Identity and Appearance. Psychol Women Q [Internet]. 2012 [cited 2024 Jan 10];36:179–96. Available from: https://journals-sagepub-com.zorac.aub.aau.dk/doi/pdf/10.1177/0361684312442161

56. Testa RJ, Habarth J, Peta J, Balsam K, Bockting W. Development of the Gender Minority Stress and Resilience Measure. Psychol Sex Orientat Gend Divers [Internet]. 2015 [cited 2024 Jan 10];2:65–77. Available from: https://psycnet-apa-org.zorac.aub.aau.dk/fulltext/2014-57149-

001.pdf?sr=1&fbclid=IwAR2FVMi0TZQgeu6VFgzkytAqPFQiZQzzxlveWsxdA35dW3o
VXdrPILrk7Xk

57. THE WHOQOL GROUP. Development of the World Health Organization WHOQOL-
     BREF Quality of Life Assessment. Psychol Med. 1998;28:551–8.

58. WHO. WHOQoL-Bref [Internet]. 2002 [cited 2024 Jan 12]. Available from: Danish-
     WHOQOL-BREF_new.pdf

59. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data
     capture (REDCap)—A metadata-driven methodology and workflow process for providing
     translational research informatics support. J Biomed Inform. 2009;42:377–81.

60. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap
     consortium: Building an international community of software platform partners. J Biomed
     Inform. 2019;95:103208.

61. Finnerty A. Danish_WHOQOL-BREF [Internet]. 2020 [cited 2024 Apr 8]. Available
     from: https://www.who.int/tools/whoqol/whoqol-bref/docs/default-source/publishing-
     policies/whoqol-bref/danish-whoqol-bref

62. University of Washington Seattle, Oliver M. WHOQOL-BREF U.S. Version. Washington
     United States of America; 1997.

63. Programme on mental health WHOG. WHOQOL-BREF Introduction, Administration,
     Scoring and Generic Version of the Assessment. 1996 Dec.

64. van Leerdam TR, Zajac JD, Cheung AS. The Effect of Gender-Affirming Hormones on
     Gender Dysphoria, Quality of Life, and Psychological Functioning in Transgender
     Individuals: A Systematic Review. Transgend Health. 2023;8:6–21.

65. Gómez-Gil E, Zubiaurre-Elorza L, Esteva de Antonio I, Guillamon A, Salamero M.
     Determinants of quality of life in Spanish transsexuals attending a gender unit before
     genital sex reassignment surgery. Quality of Life Research. 2014;23:669–76.

66. Manieri C, Castellano E, Crespi C, Di Bisceglie C, Dell'Aquila C, Gualerzi A, et al.
     Medical Treatment of Subjects with Gender Identity Disorder: The Experience in an
     Italian Public Health Center. International Journal of Transgenderism. 2014;15:53–65.

67. Gorin-Lazard A, Baumstarck K, Boyer L, Maquigneau A, Gebleux S, Penochet JC, et al.
     Is Hormonal Therapy Associated with Better Quality of Life in Transsexuals? A Cross-
     Sectional Study. J Sex Med. 2012;9:531–41.

68. Bultynck C, Pas C, Defreyne J, Cosyns M, den Heijer M, T'Sjoen G. Self-perception of
     voice in transgender persons during cross-sex hormone therapy. Laryngoscope.
     2017;127:2796–804.

69. Sundhedsstyrelsen. Øvre og nedre kønsmodificerende kirurgi - Faglig
     visitationsretningslinje [Internet]. København S; 2023 Oct. Available from: www.sst.dk

70. Simbar M, Nazarpour S, Mirzababaie M, Emam Hadi MA, Ramezani Tehrani F, Alavi Majd H. Quality of Life and Body Image of Individuals with Gender Dysphoria. J Sex Marital Ther. 2018;44:523–32.

71. Filipov H, Kavla Y, Şahin S, Gökler ME, Turan Ş. The Effects of Gender-Affirming Hormone Therapy on Body Satisfaction, Self-Esteem, Quality of Life, and Psychopathology in People with Female-to-Male Gender Dysphoria. Transgend Health. 2023;8:168–74.

72. Skovlund CW, Mørch LS, Kessing LV, Lidegaard Ø. Association of Hormonal Contraception With Depression. JAMA Psychiatry. 2016;73:1154.

73. Martell S, Marini C, Kondas CA, Deutch AB. Psychological side effects of hormonal contraception: a disconnect between patients and providers. Contracept Reprod Med. 2023;8:9.

74. Brønnick MK, Økland I, Graugaard C, Brønnick KK. The Effects of Hormonal Contraceptives on the Brain: A Systematic Review of Neuroimaging Studies. Front Psychol. 2020;11.

75. Miller KK, Perlis RH, Papakostas GI, Mischoulon D, Iosifescu D V., Brick DJ, et al. Low-dose Transdermal Testosterone Augmentation Therapy Improves Depression Severity in Women. CNS Spectr. 2009;14:688–94.

76. Hermans EJ, Putman P, Baas JM, Koppeschaar HP, van Honk J. A Single Administration of Testosterone Reduces Fear-Potentiated Startle in Humans. Biol Psychiatry. 2006;59:872–4.

77. Rohr UD. The impact of testosterone imbalance on depression and women's health. Maturitas. 2002;41:25–46.

7. Appendix

7.1 QoL Scores for Patients Receiving GAHT and Controls for Assigned Sex at Birth Groups

	AMAB			AFAB		
	GAHT	Control		GAHT	Control	
n (%)	143	26		141	50	
QoL			p-values			p-values
D1	59.8	58.4	0.699	63.0	57.1	0.065
D2	51.4	36.9	0.003**	53.9	44.3	0.004**
D3	57.5	54.5	0.552	65.4	65.2	0.949
D4	62.6	55.4	0.063	66.6	61.9	0.099

*Figure 4. Mean Quality of Life (QoL) Scores for each domain (D1: physical; D2: psychological; D3: social; D4: environmental) for patients receiving gender-affirming hormone therapy (GAHT) and controls for both patients assigned male at birth (AMAB) and patients assigned female at birth (AFAB). ** Indicates a significance level <0.01.*

7.2 QoL Scores for Patients AMAB and AFAB in the GAHT and Control Group

	GAHT Group			Control Group		
	AMAB	AFAB		AMAB	AFAB	
n (%)	143	141		26	50	
QoL			p-values			p-values
D1	59.8	63.0	0.126	58.4	57.1	0.779
D2	51.4	53.9	0.310	36.9	44.3	0.146
D3	57.5	65.4	0.001**	54.5	65.2	0.059
D4	62.6	66.6	0.053	55.4	61.9	0.125

*Figure 5. Mean Quality of Life (QoL) Scores for each domain (D1: physical; D2: psychological; D3: social; D4: environmental) for patients assigned male at birth (AMAB) and patients assigned female at birth (AFAB) in the gender-affirming hormone therapy (GAHT) group and the control group. ** Indicates a significance level <0.01.*