Hormones and Behavior 110 (2019) 29–39

Contents lists available at ScienceDirect

Hormones and Behavior

journal homepage: www.elsevier.com/locate/yhbeh

No correlation between serum testosterone levels and state-level anger intensity in transgender people: Results from the European Network for the Investigation of Gender Incongruence

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ARTICLE INFO

Keywords:
Transgender
Gender affirming hormonal treatment
Testosterone
Anger
STAXI-2 questionnaire

ABSTRACT

Introduction: Anger is a state of emotions ranging from irritation to intense rage. Aggression implies externalizing anger through destructive/punitive behaviour. The World Professional Association for Transgender Health (WPATH) Standards of Care, Edition 7 (SOC7) guidelines warn about aggression in transgender men (TM) on testosterone treatment. We aimed to assess whether anger intensity increases in TM and decreases in transgender women (TW) after initiation of gender affirming hormone therapy and to identify predictors for anger intensity in transgender people.

Methods: This prospective cohort study was part of the European Network for the Investigation of Gender Incongruence (ENIGI). Anger intensity was prospectively assessed in 898 participants (440 TM, 468 TW) by STAXI-2 (State-Trait Anger Expression Inventory-2) State Anger (S-Anger) during a three-year follow-up period, starting at the initiation of hormone treatment. Data were analysed cross-sectionally and prospectively.

Results: There was no change in STAXI-2 S-Anger scores. At three, twelve and thirty-six months of gender affirming hormone therapy, STAXI-2 S-Anger scores were not correlated to serum testosterone levels, although there was a correlation with various psychological measures after three and twelve months. TM experiencing menstrual spotting after three months had higher STAXI-2 S-Anger scores compared to those without (median 26.5 [18.0–29.8] versus 15.0 [15.0–17.0], P = 0.020).

Changes in STAXI-2 S-Anger scores were not correlated to changes in serum testosterone levels after three, twelve and thirty-six months in TM or TW.

Conclusions: State-level anger intensity is associated with psychological and/or psychiatric vulnerability, but not exogenous testosterone therapy or serum testosterone levels in transgender people.

1. Introduction

In 2007, four major European gender clinics initiated a research cooperative; the 'European Network for the Investigation of Gender Incongruence' (ENIGI). Within ENIGI, a uniform psychological and endocrinological protocol has been designed, which includes a standard battery of questionnaires and a common endocrinological protocol for treatment and follow-up. (Dekker et al., 2016; Kreukels et al., 2012)

Transgender people are individuals whose sex assigned at birth does not match with their current gender identity. If desired, options for gender affirming treatment in transgender individuals include social transitioning, gender affirming hormonal therapy and/or gender

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https://doi.org/10.1016/j.yhbeh.2019.02.016
Received 7 November 2018; Received in revised form 25 February 2019; Accepted 25 February 2019

affirming surgery. Hormonal therapy in transgender men (TM) may consist of testosterone agents, administered orally, intramuscularly or transdermally. Testosterone therapy leads to an overall satisfactory masculinization in the daily life of TM (Fisher et al., 2016, 2014). To obtain amenorrhea in TM who have not undergone hystero-oophorectomy, a progestin or a gonadotropin-releasing hormone (GnRH) agonist can be added to the treatment regimen (Hembree et al., 2017). The current hormonal treatments for transgender women (TW) usually involve oestrogens (administered orally or transdermally) and anti-androgens (to suppress testosterone levels and decrease masculine secondary sexual characteristics) (Dekker et al., 2016). Gender affirming hormonal therapy is continued life-long to maintain virilisation in TM and feminization in TW, independent of genital surgery. However, if orchiectomy is desired, anti-androgens can be discontinued post-operatively.

Research has concluded that gender affirming therapy generally leads to high satisfaction rates (Defreyne et al., 2017), an increase in quality of life and a decrease in gender dysphoria, body uneasiness, depressive and anxiety symptoms, somatization, interpersonal sensitivity, hostility and general psychopathology (Murad et al., 2010). Cross sectional studies comparing transgender people on gender affirming hormones with those without, report lower subjective levels of gender dysphoria, body uneasiness, anxiety and depressive symptoms in those on gender affirming hormones. The majority of transgender people on gender affirming therapy are functioning well psychologically, socially and sexually (Bartolucci et al., 2015; Murad et al., 2010; White Hughto and Reisner, 2016).

Despite these findings, publications, such as 'A psycho-endocrinological overview of transsexualism' (2001) (Michel et al., 2001), and the World Professional Association for Transgender Health (WPATH) Standards of Care, edition 7 (SOC 7)(2011) (WPATH, 2012) warn for aggression in TM as an unfavourable side effect of testosterone therapy, that may be related to cyclical variation. This advice is based upon their clinical experience and two manuscripts. One manuscript from 1995 assessed prospective differences in anger and aggression in 35 TM and 15 TW over a period of 3 months (Van Goozen et al., 1995), finding an increase in proneness to anger and aggression in both groups. One review article from 2003 mentioned one study observing 'aggression and hypersexuality' as adverse effects of gender-affirming hormonal therapy in TM (Moore et al., 2003).

It is known that testosterone promotes aggressive behaviour in male animals (Delville et al., 1996; Fuxjager et al., 2016; Wingfield et al., 1987). In castrated rodents, showing a near-complete absence of physical fights, fighting is reinitiated after the administration of exogenous testosterone (Beeman, 1947). In some female mammals, testosterone administration also results in aggressive behaviour (Albert et al., 1989; Frank et al., 1991; Gray et al., 1978), although research on androgens in female animals is scarce (Archer, 2006; Sandnabba et al., 1994).

Studies describing a positive relationship between aggression and endogenous testosterone in humans have primarily been conducted in aggression-prone cisgender male populations, such as prison inmates (Dabbs Jr et al., 1987; Kreuz and Rose, 1972) or after a competitive or provocating study task (Carré et al., 2009; Wagels et al., 2018). In cisgender women, there appears to be no correlation between aggression and endogenous serum testosterone levels (Carré et al., 2009). To date, research on the relationship between testosterone administration and aggression in humans is often inconclusive (Eisenegger et al., 2011; O'Connor et al., 2002; Panagiotidis et al., 2017) and the administered dose of testosterone often results in supraphysiological levels of serum testosterone (Dreher et al., 2016). It is also possible that exogenous testosterone administration on its own does not potentiate provoked aggressive behaviour, but is mediated by trait dominance and trait self-control (Carré et al., 2017). Recent research in transgender people contradicts guidelines mentioning aggression as a side effect in TM on testosterone therapy, as no increase in aggression was observed in TM one year after the initiation of testosterone therapy (Defreyne et al., 2018).

Anger differs from aggression, as the latter generally implies externalizing angry emotions as verbal, destructive or punitive behaviour directed towards other people or objects (Spielberger et al., 1983). Anger was defined by Spielberger as 'an emotional state that consists of feelings that vary in intensity, from mild irritation or annoyance to intense fury and rage'(Spielberger et al., 1983). Thomas et al. have stated that men and women have different ways of experiencing and expressing anger (Thomas, 1993, 1989). No difference was found in anger-suppression or –expression, but women are more likely to discuss their anger and have more anger-related symptoms. Kopper and Epperson also did not find any gender differences in general predisposition to become angry (trait anger), suppression (anger-in) or externalization (anger-out) of angry feelings and controlling the physical or verbal expressions of anger (anger-control) (Kopper and Epperson, 1991). However, previous research concluded that men (or people with a male gender role) score higher on trait anger, anger expression and have lower anger control scores, compared to women (or those with a female gender role) (Bem, 1981; Spielberger et al., 1995). Results on the relationship between exogenous testosterone and anger are again inconclusive in cisgender men. Whereas Wagels et al. (Wagels et al., 2018) reported no increased state anger as measured by the State-Trait Anger Expression Inventory (STAXI), after application of testosterone gel in cisgender men, Panagiotidis et al. (Panagiotidis et al., 2017) reported a potentiating effect of testosterone gel administration on anger experience after provocation. Research on the relationship between testosterone administration and anger in transgender people is based on small study samples. One older study that included 35 TM reported a prospective increase in anger proneness three months after the initiation of gender affirming hormonal therapy (Van Goozen et al., 1995). A more recent study with 52 TM also reported an increase in the number of TM reporting higher anger expression 7 months after the initiation of testosterone treatment (Motta et al., 2018). The observed increase in anger expression correlated with persistent bleeding and presence of Diagnostic and Statistical Manual of Mental Disorders (DSM) Axis 1 disorders but not with serum testosterone levels. As both studies are based on small samples of short duration, anger should be assessed in a large group of transgender people during a longer follow-up period.

The overall aim of this study was to prospectively examine whether exogenous testosterone therapy increases anger intensity in TM and whether oestrogen plus anti-androgen therapy reduces anger intensity in TW. Based on our clinical experience and one previous manuscript stating that measurements of aggression do not change after the initiation of gender affirming hormone therapy in TM or TW (Defreyne et al., 2018), we hypothesized that serum testosterone levels do not correlate with self-reported levels of anger intensity, nor does exogenous testosterone increase anger intensity or do anti-androgens decrease anger intensity. We were also interested in identifying any psychological/psychiatric predictors for anger intensity, with particular interest in body image, symptoms of psychopathology, positive and negative affect, quality of life, experienced gender dysphoria and psychiatric morbidity.

2. Methods

2.1. Participants

Transgender people first visited a psychologist or psychiatrist associated with the ENIGI study. During this phase, various psychological questionnaires were administered. More information on the psychological protocol of the ENIGI initiative was previously published (Kreukels et al., 2012). Upon indication, transgender persons are referred to the endocrinology department (if requested). In total, 1669 people were included in the endocrinological part of the ENIGI study, which started in 2010 (1055 in Amsterdam, 357 in Ghent, 67 in Florence and 190 in Oslo). The study protocol of the endocrinological part

of ENIGI was also previously published (Dekker et al., 2016). A written informed consent was obtained according to the institution's guidelines. The STAXI-2 S-Anger assessment was added to the battery of questionnaires in September 2012. In Ghent, 93 participants did not fill in the STAXI-2 questionnaire, as they were included in the ENIGI protocol before the addition of this questionnaire. Participants in Florence and Oslo did not complete the STAXI-2 questionnaire. Data from only 708 participants was entered into the database in Amsterdam (of which 74 participants did not fill in the STAXI-2 S-Anger at baseline), whereas in Ghent, data was entered from all participants who completed the survey. In total, 898 participants who filled in the STAXI-2 questionnaire at baseline were included in this prospective analysis.

2.2. Gender affirming hormone therapy

A baseline assessment was performed by the mental health professional. All patients were 16 years and older and underwent a standardized diagnostic procedure to confirm the diagnosis of gender incongruence/gender dysphoria before initiating treatment. After baseline assessment, gender affirming hormone therapy was initiated according to the ENIGI study protocol. In Ghent, TM received intramuscular long-acting testosterone undecanoate (Nebido® 1000 mg once every 12 weeks). In Amsterdam, TM could choose between testosterone gel in a daily dose of 50 mg or intramuscular administration, either as testosterone esters (Sustanon® 250 mg every 2 weeks) or testosterone undecanoate (Nebido® 1000 mg every 12 weeks). All TM in the 36-month follow-up group were on testosterone undecanoate. In TW, estrogens plus anti-androgens are administered. Anti-androgen therapy consisted of cyproterone acetate 25 to 50 mg once daily (Androcur®, Bayer, Diegem, Belgium and Androcur®, Bayer, Mijdrecht, the Netherlands). Oestrogen therapy generally consisted of oestradiol valerate 2 mg (Progynova®, Bayer, Diegem, Belgium and Progynova®, Bayer, Mijdrecht, the Netherlands) twice daily. In patients older than 45 years of age, oestradiol was administered transdermally in the form of oestradiol patches (Dermestril®, Besins, Brussels, Belgium or Systen®, Bayer, Mijdrecht, the Netherlands) in a dose of 100 μg/72 h, to avoid the increased risk for thrombosis from oral oestrogens caused by the first pass effect of the liver. In case of intolerance, oestrogens were administered as gel (Oestrogel®, Besins) in a dose of 1.5 mg twice daily.

2.3. Main outcome measures: psychological battery assessed only at baseline

The Body Image Scale for evaluating transsexuals (BIS) (in Dutch or French) was used to assess the way transgender people perceive their body and how they feel about these perceptions. The scale consists of 30 body features, ranked by the participant on a five-point Likert scale of satisfaction, ranging from 'very satisfied' to 'very dissatisfied'. Internal consistency in the current sample was high (Cronbach's alpha = 0.974) (Lindgren and Pauly, 1975).

The Utrecht Gender Dysphoria Scale (UGDS) (in Dutch or French) was used to measure the degree of experienced gender dysphoria. This scale consists of 12 questions answered on a five-point Likert scale, ranging from 'completely agree' to 'completely disagree'. Internal consistency in the current sample was good (Cronbach's alpha = 0.797). (Cohen-Kettenis and van Goozen, 1997)

The Symptom Checklist 90-Revised (SCL-90R) (in Dutch or French) was used to assess self-reported psychological burden on eight symptom scales: somatization, sleeping problems, paranoid ideation/psychoticism, agoraphobia, depression, hostility, anxiety, interpersonal sensitivity and a global score 'overall psychoneurotic distress', as previously described (Arrindell and Ettema, 2003). Internal consistency in the current sample ranged from good to high for all factors (Somatization: $\alpha = 0.797$, sleeping problems: $\alpha = 0.761$, paranoid ideation/psychoticism: $\alpha = 0.868$, agoraphobia: $\alpha = 0.822$, depression: $\alpha = 0.924$, hostility: $\alpha = 0.805$, anxiety: $\alpha = 0.882$, interpersonal sensitivity: $\alpha = 0.925$, overall psychoneurotic distress: $\alpha = 0.760$).

The MINI-Plus interview (in Dutch or French) was used by the psychologist/psychiatrist to assess DSM Axis I disorders. It is a short structured diagnostic interview for DSM-IV and ICD-10 psychiatric conditions. It was designed for multicentre clinical trials. (Hergueta et al., 1998) Data were recoded to current or lifetime presence (1) and absence (0) of each disorder.

Life as a whole (Bradburn) (in Dutch or French) was used to assess general and social quality of life. General quality of life consisted of four questions, social quality of life consisted of eight questions, answered on a three point Likert scale with 'yes', 'more or less' and 'no' as possible answers, with a higher score indicating worse quality of life. (Bradburn, 1969)

2.4. Main outcome measures: prospective measures

The State-Trait Anger Expression Inventory 2 (STAXI-2) (in Dutch or French) was constructed to measure the intensity of anger as an emotional state (State Anger, S-Anger) and the disposition to experience anger as a personality trait (Trait Anger, T-Anger). It includes scales assessing S-Anger, T-Anger, anger expression and anger control. S-Anger is defined as a psychobiological state or condition consisting of subjective feelings varying in intensity, paired with activation or arousal of the autonomic nervous system (anger intensity). The S-Anger questionnaire consisted of 15 questions. All questions were answered on a 4-point Likert scale, ranging from 'almost never' (1) to 'almost always' (4). T-Anger, anger expression and anger control were not assessed. The S-Anger score was calculated by adding the scores on the individual questions (total score range 15–60) and analysed cross-sectionally as well as prospectively. T-Anger is defined as the frequency at which S-anger is experienced over time (anger disposition), assuming that persons higher in T-Anger perceive a wider range of situations as anger-provoking and more frequently experience elevations in S-Anger. Trait anger refers to a chronic, long-standing personality characteristic. To measure the effects of gender affirming hormonal therapy on anger as an emotional state (anger intensity) in transgender persons, we prospectively assessed S-Anger scores only, as T-Anger reflects a personality trait, which is less likely to change over a three-year period. The STAXI-2 S-Anger was assessed during each endocrinological follow-up visit. Internal consistency in the current sample was high (Cronbach's alpha = 0.939) (Spielberger et al., 1983). The STAXI-2 has been validated in both general and clinical populations (Lievaart et al., 2016).

The Positive and Negative Affect Schedule (PANAS) (in Dutch or French) was constructed to assess positive and negative valanced emotional states and attitudes. Positive Affect (PA) comprises feelings of enthusiasm, concentration, activity, alertness and pleasurable engagement, whereas low PA is characterized by sadness and lethargy. Negative Affect (NA) reflects the extent to which a person experiences subjective distress and unpleasurable engagement, resulting in feelings of anger, contempt, disgust, guilt, fear, nervousness. Although the terms Positive Affect and Negative Affect might suggest that these two mood factors are opposites, they are highly distinctive dimensions. The questionnaire consists of twenty questions: ten assessing PA, ten assessing NA. All questions are answered on a 4-point Likert scale, ranging from 'very slightly or not at all' (1) to 'extremely' (4). The PANAS was assessed during each endocrinological follow-up moment. Internal consistency in the current sample was high for both PA (Cronbach's alpha = 0.951) and NA (Cronbach's alpha = 0.912). (Engelen et al., 2006; Watson et al., 1988)

The Ferriman-Gallwey (FG) score is used to evaluate and quantify hirsutism in women. The FG score is the sum of scores of hair densities, which range from zero (no hair) to five (full hair growth) on nine body sites (upper lip, chin, chest, abdomen, pubic hair, upper arms, upper legs, upper back and lower back) (Ferriman and Gallwey, 1961). The FG score was assessed to measure virilisation in TM during each

endocrinological follow-up moment. Because of shaving and local manipulation, the FG score was not assessed in TW. The use of the FG score to evaluate virilisation in TM has been previously reported in Wierckx et al. (Wierckx et al., 2014) and Giltay et al. (Giltay and Gooren, 2000).

Persistence of menstruation and/or spotting was evaluated using the symptom checklist, a questionnaire designed by ENIGI to assess possible side effects of the gender affirming hormone therapy. Participants were asked to grade the severity of menstruation and spotting on a 4-point Likert scale, ranging from 0 (none) to 3 (severe). The persistence of menstruation and/or spotting was assessed in TM, during each endocrinological follow-up moment. Data were analysed both as severity (absolute scores) and as presence/absence of menstruation/spotting (0 versus 1).

2.5. Laboratory analyses

Laboratory analyses were performed during each study visit, starting from the baseline visit. In both Ghent and Amsterdam a competitive chemiluminescent immunoassay was run for oestradiol (E170 Modular, Roche, Gen III, LOQ 25 pg/mL, interassay CV 3.2%), and for sex hormone binding globulin (SHBG), a sandwich type chemiluminescent immunoassay was employed (E170 Modular, Roche, Gen III, interassay CV 4.06%, LOQ 0.35 mIU/mL).

In Ghent, competitive chemiluminescent immunoassays were used to measure testosterone (E170 Modular, Roche, Gen II, LOQ 10 ng/dL (0.4 nmol/L), interassay CV 2.6%), luteinizing hormone (LH) (E170 Modular, Roche, Gen III, interassay CV 3.48%, LOQ 0.1mIU/mL) and follicle stimulating hormone (FSH) (E170 Modular, Roche, Gen III, interassay CV 3.3%, LOQ 0.1 mIU/mL), whereas Amsterdam used a competitive immunoassay for testosterone (Architect, Abbott, Abbott Park, IL, USA) with an interassay CV of 6%–10% and a LOQ of 0.1 nmol/L, and chemiluminescent microparticle immunoassays for LH, FSH and SHBG (Architect system, Abbott), with an interassay CV of 4% and a LOQ of 2 U/L for LH, FSH and SHBG (Wiepjes et al., 2017). In Ghent, SHBG was measured using a sandwich type chemiluminescent immunoassay (E170 Modular, Roche, Gen III, interassay CV 4.06%, LOQ 0.35 mIU/mL).

In both Ghent and Amsterdam, oestradiol was measured using a E170 Modular (Gen II, Roche Diagnostics, Mannheim, Germany) until March 19, 2015 and testosterone was measured using a radioimmunoassay (RIA) (Coat-A-Count, Siemens, Los Angeles, CA, USA) until January 2013. For conversion of oestradiol values measured before March 19, 2015, the formula Gen III = 6.687940 + 0.834495 * Gen II was used. For testosterone levels below 8 nmol/L, the formula Architect = 1.1 * RIA + 0.2 was used to convert the testosterone values; for testosterone levels above 8 nmol/L, the formula Architect = 1.34 * RIA – 1.65 was used (Wiepjes et al., 2017).

2.6. Statistical analyses

Data were analysed prospectively over the entire follow-up period (STAXI-2 S-Anger scores at thirty-six months – STAXI-2 S-Anger scores at baseline), over one year of follow-up (twelve months – baseline) and over three months of follow-up (three months –baseline) (Fig. 1). The three-month timeframe was chosen to provide an insight in the trend towards an increase in anger proneness in TM during the first three months. In order to evaluate anger proneness on a longer follow up period, both the twelve-month and thirty-six-month timeframe were used, as follow-up only consisted of one year in Amsterdam. We attempted to analyse prospective data using generalized linear mixed models analysis in SPSS statistics (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

Data for total STAXI-2 S-Anger scores was skewed and non-transformable. Unfortunately, we were not able to construct a model. Therefore, data were prospectively assessed as the increase in anger intensity over time (total STAXI-2 S-Anger score at given time point – baseline total STAXI-2 S-Anger score). Prospective data were analysed using Friedman's test or Wilcoxon's signed rank test for continuous non-normally distributed data. For categorical variables, the difference between prospective STAXI-2 S-Anger scores between the groups was assessed by Mann-Whitney *U* test (two independent samples) or Kruskal-Wallis H test (n independent samples). For continuous variables, correlations with prospective total STAXI-2 S-Anger scores were assessed by Spearman's Rho correlation coefficient. To control for differences in testosterone mode of administration and laboratory analyses of serum testosterone levels, all statistics were re-tested in groups using the same type of testosterone as well as groups in whom serum testosterone levels were analysed using the same method.

For normally distributed data, values are shown as mean ± standard deviation (SD), for not-normally distributed data, values are shown as median [percentile 25 – percentile 75]. To elaborate the observed trend towards an increase in anger intensity in TM after three months, again decreasing after twelve months, cross-sectional analyses (correlations using Spearman's Rho, differences between groups using Mann-Whitney U) were performed on the 3, 12 and 36 months follow-up data. Significant results are indicated with *, if required, a Bonferroni-Holm correction was applied to adjust for multiple comparisons (Holm, 1979), which explains why some P-values < 0.05 are not being marked as significant.

3. Results

From February 2010 until July 2017, 898 participants (Amsterdam 634; 317 TW, 317 TM, Ghent 264; 152 TW, 112 transgender men) filled in the STAXI-2 S-Anger questionnaire at baseline. Baseline statistics are shown in Table 1. Median age of all participants was 24 years old [20–34]. TM were significantly younger than TW (22.0 [20.0–27.0] versus 28.0 [22.0–41.0], P < 0.001*), but there was no difference in ages between the two centres (TM P = 0.140, TW P = 0.141). Baseline STAXI-2 S-Anger scores were comparable in TW and TM (15.0 [15.0–16.8] and 15.0 [15.0–16.0], P = 0.777). There was no difference in baseline STAXI-2 S-Anger scores in TM or TW at the different centres (P = 0.621 and P = 0.213 for TW and TM, respectively).

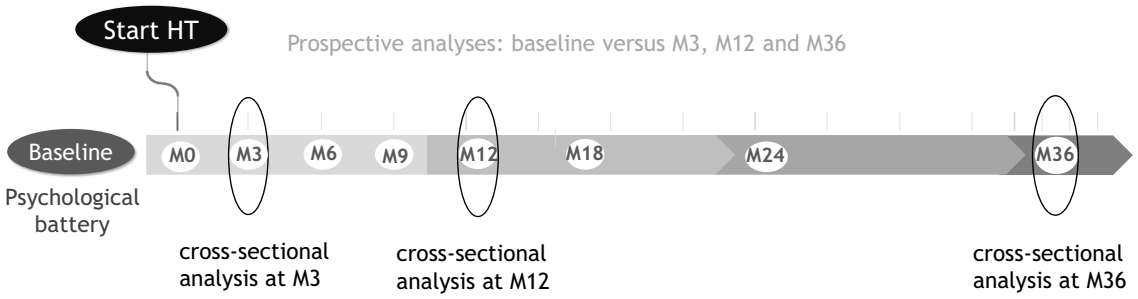

Fig. 1. Methodology of the cross-sectional and prospective analyses over the study follow-up duration (months).

Table 1
Baseline characteristics of the study population, subdivided by gender identity (TM = transgender men, TW = transgender women). Differences between groups were tested by Mann-Whitney *U* test for non-parametric values. Frequencies of co-occurring morbidities in the two gender groups were compared using Fisher's exact test. Significant differences between both groups are indicated in bold (P-value). Differences that remained significant after Bonferroni-Holm correction are indicated with *.

	TM (429)	TW (469)	Total (908)	Difference (P-value)
Age	22.0 [20.0–27.0]	28.0 [22.0–41.0]	24.0 [20.0–34.0]	**P < 0.001***
Total STAXI-2 scores	15.0 [15.0–16.0]	15.0 [15.0–16.8]	15.0 [15.0–16.0]	P = 0.777
Number of transgender men reporting menstruation (%)(202 missing)	39 (16.4%)	/	/	/
Number of transgender men reporting spotting (%) (198 missing)	31 (12.8%)			
Number of transgender men using contraceptives (%)	72 (15.2%)			
Median Ferriman-Gallwey score	1.0 [0.0–3.0]			
Gender affirming hormonal therapy				
Testosterone				
AG 25 mg once daily	21 (5.3%)	/	/	/
AG 50 mg once daily	120 (30.5%)			
TU 1 g once every 12 weeks	128 (32.6%)			
TE once every 2 weeks	122 (31.0%)			
TE once every 3 weeks	2 (0.5%)			
Anti-androgens				
CPA 50	/	430 (99.5%)	/	/
CPA 100		1 (0.2%)		
Oestrogens				
Gel	/	4 (1.0%)		
EV		241 (57.8%)		
Patch 100 μg/72 h		152 (36.5%)		
Patch 50 μg/72 h		18 (4.3%)		
Patch 75 μg/72 h		2 (0.5%)		
Serum testosterone levels (nmol/L)	1.2 [0.9–1.6]	18.4 [14.0–23.1]	7.3 [1.3–19.4]	**P < 0.001***
Serum oestradiol levels (pg/mL)	101.0 [34.6–239.3]	68.4 [30.6–95.6]	76.0 [33.0–119.0]	**P < 0.001***
Serum LH levels (U/L)	4.5 [2.4–7.7]	3.9 [2.7–5.3]	4.1 [2.7–9.8]	**P = 0.004**
Serum FSH levels (U/L)	5.6 [3.3–7.2]	3.5 [2.3–4.9]	4.0 [2.5–6.3]	**P < 0.001***
Serum SHBG levels (ng/dL)	54.7 [35.0–81.0]	36.8 [26.7–51.3]	41.7 [29.7–62.4]	**P < 0.001***
Median PANAS scores				
Positive affect	33.0 [27.0–38.0]	33.0 [27.0–37.0]	33.0 [28.0–38.0]	P = 0.902
Negative affect	14.0 [12.0–19.0]	14.0 [12.0–19.0]	14.0 [12.0–19.0]	P = 0.897
Median body image scale (BIS) scores	97.0 [82.0–106.0]	101.0 [89.0–113.0]	101 [91.0–111.0]	**P = 0.003**
Median quality of life (QOL) scores				
Total	8.0 [7.0–9.0]	8.0 [7.0–9.0]	8.0 [7.0–9.0]	P = 0.135
Social	30.0 [26.0–34.0]	30.0 [26.0–33.0]	30.0 [26.0–34.0]	P = 0.722
Median total SCL-90-R, Symptom Checklist scores (SCL-90R)				
Total	23.0 [10.0–54.0]	23.0 [8.0–47.3]	23.0 [9.0–51.0]	P = 0.512
Somatization	4.0 [1.0–8.0]	2.5 [1.0–6.0]	3.0 [1.0–7.0]	**P < 0.001***
Sleeping problems	2.0 [0.0–4.0]	1.0 [0.0–4.0]	2.0 [0.0–4.0]	**P = 0.021**
Paranoid ideation	4.5 [2.0–9.0]	4.0 [1.0–8.0]	4.0 [1.0–8.0]	P = 0.049
Hostility	1.0 [0.0–3.0]	1.0 [0.0–2.0]	1.0 [0.0–2.0]	**P = 0.003**
Depression	6.0 [2.0–15.0]	8.0 [3.0–16.0]	7.0 [3.0–15.0]	P = 0.097
Anxiety	2.0 [0.0–7.0]	2.0 [0.0–5.8]	2.0 [0.0–5.0]	P = 0.757
Interpersonal sensitivity	5.0 [1.0–13.0]	6.0 [1.0–14.3]	5.0 [1.0–12.0]	P = 0.503
Overall psychoneurotic distress	2.0 [0.0–4.8]	2.0 [0.0–5.0]	2.0 [0.0–4.0]	P = 0.505
The MINI-PLUS assessment: number of participants with current/previous… (%) (130 missing)				
Depressive episode	134 (35.4%)	131 (33.9%)	265 (34.5%)	P = 0.350
Dysthymia	25 (6.6)	30 (7.8%)	55 (7.2%)	P = 0.577
Suicidality	80 (21.0%)	74 (19.1%)	154 (20.1%)	P = 0.288
Manic episode	6 (1.6%)	9 (2.3%)	15 (2.0%)	P = 0.604
Panic disorder	35 (9.2%)	34 (8.8%)	69 (9.0%)	P = 0.900
Agoraphobia	26 (6.8%)	24 (6.2%)	50 (6.5%)	P = 0.771
Social phobia	19 (5.0%)	25 (6.5%)	44 (5.7%)	P = 0.439
Phobia	9 (2.4%)	11 (2.8%)	20 (2.6%)	P = 0.822
Obsessive-Compulsive disorder	9 (2.4%)	7 (1.8%)	16 (2.1%)	P = 0.623
Posttraumatic disorder	4 (1.0%)	5 (1.3%)	9 (1.1%)	P = 1.000
Alcohol dependence/abuse	10 (2.6%)	12 (3.1%)	22 (2.9%)	P = 0.829
Substance dependence/abuse	25 (6.6%)	21 (5.4%)	46 (6.0%)	P = 0.545
Psychotic disorder	6 (1.6%)	6 (1.6%)	12 (1.6%)	P = 1.000
Anorexia nervosa	0	0	0	/
Bulimia nervosa	0	1 (0.3%)	1 (0.1%)	P = 1.000
Generalized panic disorder	10 (2.3%)	9 (2.3%)	19 (2.5%)	P = 0.820
Antisocial personality disorder	0	0	0	/
Somatization disorder	2 (0.5%)	0	2 (0.3%)	P = 0.246
Hypochondria	0	2 (0.5%)	2 (0.3%)	P = 0.499
Body dismorphic disorder	2 (0.5%)	4 (1.0%)	6 (0.8%)	P = 0.686
Pain disorder	0	2 (0.5%)	2 (0.3%)	P = 0.499
Conduct disorder	0	0	0	/
Attention deficit with hyperactivity	19 (5.0%)	6 (1.6%)	25 (3.3%)	**P = 0.008**
Conduct disorder	1 (0.3%)	0	1 (0.1%)	P = 1.000
Premenstrual dysphoria	6 (1.6%)	/	6 (0.8%)	/
Mixed anxiety-depressive disorder	0	0	0	/

Table 2
Correlations between cross-sectional scores for anger proneness during the first 3, 12 and 36 months of follow-up (total STAXI-2 S-Anger scores) and cross-sectional levels of sex steroids, virilization scores (Ferriman-Gallwey), menstruation and spotting, levels of positive and negative affect and baseline psychological evaluation (UGDS, QOL, SCL-90R, BIS). Correlations were tested using Spearman's correlation coefficient. Significant correlations are indicated in bold (P-value). Correlations that remained significant after Bonferroni-Holm correction are indicated with *. (TM = transgender men, TW = transgender women LH = luteinizing hormone, FSH = follicle stimulating hormone, SHBG = sex steroid binding hormone, UGDS = Utrecht Gender Dysphoria Scale, QOL = quality of life, SCL-90R = SCL-90R Symptom Checklist, BIS = Body Image Scale).

Cross-sectional correlations with total STAXI-2 scores						
	TM			TW		
	3 months	12 months	36 months	3 months	12 months	36 months
	Δ total STAXI-2 scores	Δ total STAXI-2 scores	Δ total STAXI-2 scores	Δ total STAXI-2 scores	Δ total STAXI-2 scores	Δ total STAXI-2 scores
Total STAXI-2 scores	/	/	/	ρ = −0.27 P = 0.251	/	/
Serum testosterone levels	ρ = **−0.14** **P = 0.031**	ρ = −0.04 P = 0.599	ρ = −0.44 P = 0.280	ρ = **0.15** **P = 0.017**	ρ = 0.07 P = 0.313	ρ = 0.40 P = 0.082
Serum oestradiol levels	ρ = −0.03 P = 0.610	P = 0.08 P = 0.235	ρ = −0.40 P = 0.326	ρ = −0.02 P = 0.719	ρ = −0.04 P = 0.546	ρ = −0.30 P = 0.183
Serum LH levels	ρ = 0.09 P = 0.167	P = 0.04 P = 0.550	ρ = 0.37 P = 0.373	ρ = 0.08 P = 0.246	ρ = 0.06 P = 0.356	ρ = 0.07 P = 0.759
Serum FSH levels	ρ = −0.05 P = 0.781	P = 0.03 P = 0.807	ρ = 0.41 P = 0.306	ρ = −0.12 P = 0.542	ρ = −0.13 P = 0.239	ρ = 0.06 P = 0.803
Serum SHBG levels	ρ = 0.02 P = 0.878	P = 0.02 P = 0.833	ρ = −0.11 P = 0.797	ρ = −0.07 P = 0.495	ρ = 0.09 P = 0.308	ρ = 0.17 P = 0.438
Ferriman-Gallwey	ρ = 0.052 P = 0.430	/	/	/	/	/
Menstruation	ρ = −0.014 P = 0.870	/	/	/	/	/
Spotting	ρ = 0.006 P = 0.946	/	/	/	/	/
PANAS positive affect	ρ = **0.12** **P = 0.038**	ρ = 0.02 P = 0.812	ρ = −0.12 P = 0.652	ρ = **−0.13** **P = 0.028**	ρ = −0.06 P = 0.325	ρ = 0.27 P = 0.137
PANAS negative affect	ρ = **0.65** **P < 0.001***	ρ = **0.43** **P < 0.001***	ρ = 0.68 P = 0.003	ρ = **−0.57** **P < 0.001***	ρ = **−0.60** **P < 0.001***	ρ = **0.54** **P = 0.001***
Baseline UGDS	ρ = −0.14 P = 0.058	ρ = −0.06 P = 0.449	ρ = **−0.59** **P = 0.042**	ρ = 0.42 P = 0.231	ρ = −0.19 P = 0.160	ρ = **0.50** **P = 0.029**
Total baseline QOL	ρ = **−0.30** **P < 0.001***	ρ = −0.08 P = 0.332	ρ = −0.06 P = 0.855	ρ = −0.14 P = 0.064	ρ = −0.09 P = 0.246	ρ = −0.09 P = 0.711
Baseline social QOL	ρ = −0.13 P = 0.076	ρ = −0.01 P = 0.932	ρ = −0.03 P = 0.942	ρ = **−0.22** **P = 0.004***	ρ = 0.12 P = 0.131	ρ = −0.19 P = 0.481
Baseline SCL90-R	ρ = **0.29** **P < 0.001***	ρ = **0.26** **P = 0.009**	/	ρ = **0.33** **P < 0.001***	ρ = **0.25** **P = 0.010**	/
Baseline SCL90-R somatization	ρ = **0.22** **P = 0.003***	ρ = **0.27** **P < 0.001***	ρ = −0.19 P = 0.557	ρ = **0.28** **P < 0.001***	ρ = **0.24** **P = 0.002***	ρ = 0.12 P = 0.638
Baseline SCL90-R sleeping problems	ρ = **0.20** **P = 0.007**	ρ = 0.13 P = 0.094	ρ = 0.20 P = 0.528	ρ = **0.28** **P < 0.001***	ρ = **0.16** **P = 0.036**	ρ = 0.15 P = 0.545
Baseline SCL90-R overall psychoneurotic distress	ρ = 0.15 P = 0.063	ρ = 0.07 P = 0.495	/	ρ = **0.18** **P = 0.020**	ρ = 0.18 P = 0.060	/
Baseline SCL90-R paranoid ideation/ psychoticism	ρ = **0.26** **P < 0.001***	ρ = 0.11 P = 0.156	ρ = 0.15 P = 0.651	ρ = **0.31** **P < 0.001***	ρ = **0.17** **P = 0.026**	ρ = −0.12 P = 0.648
Baseline SCL90-R hostility	ρ = **0.29** **P < 0.001***	ρ = 0.15 P = 0.060	ρ = −0.17 P = 0.558	ρ = **0.33** **P < 0.001***	ρ = **0.21** **P = 0.007**	ρ = 0.02 P = 0.945
Baseline SCL90-R depression	ρ = **0.28** **P < 0.001***	ρ = 0.15 P = 0.063	ρ = −0.33 P = 0.295	ρ = **0.27** **P < 0.001***	ρ = **0.21** **P = 0.007**	ρ = −0.19 P = 0.446
Baseline SCL90-R anxiety	ρ = **0.25** **P = 0.001***	ρ = **0.23** **P = 0.017**	/	ρ = **0.22** **P = 0.004**	ρ = 0.17 P = 0.084	/
Baseline SCL90-R Interpersonal sensitivity	ρ = **0.35** **P < 0.001***	ρ = 0.13 P = 0.086	ρ = −0.23 P = 0.478	ρ = **0.26** **P < 0.001***	ρ = **0.21** **P = 0.007**	ρ = 0.08 P = 0.757
Baseline BIS	ρ = 0.11 P = 0.203	ρ = −0.12 P = 0.157	ρ = −0.27 P = 0.405	ρ = 0.07 P = 0.403	ρ = −0.06 P = 0.532	ρ = 0.10 P = 0.700

3.1. Cross-sectional data

3.1.1. Cross-sectional data: 3 months of follow-up

In TM, after three months of follow-up, there was no correlation between total STAXI-2 S-Anger scores and serum testosterone levels (ρ = −0.135, P = 0.031, independent of type of testosterone therapy, P-values range: 0.139–0.990) or age (ρ = −0.01, P = 0.857) (Table 2). Type of hormonal treatment did not influence STAXI-2 S-Anger scores (P = 0.104). STAXI-2 S-Anger scores were correlated with baseline poor quality of life scores (ρ = 0.29, P < 0.001*) and scores for the SCL-90R factors somatization (ρ = 0.22, P = 0.003*), paranoid ideation/psychoticism (ρ = 0.26, P < 0.001*), hostility (ρ = 0.29, P < 0.001*), depression (ρ = 0.28, P < 0.001*), anxiety (ρ = 0.25, P = 0.001*) and interpersonal sensitivity (ρ = 0.35, P < 0.001*). After partially controlling for quality of life, total SCL-90R scores and SCL-90R scores for the factors somatization, paranoid ideation/psychoticism, hostility, depression, anxiety and interpersonal sensitivity, there was no correlation between serum testosterone levels and total STAXI-2 S-Anger scores (P = 0.975).

In addition, TM who still experienced spotting had higher total

STAXI-2 S-Anger scores compared to TM without spotting (26.5 [18.0–29.8] versus 15.0 [15.0–17.0], P = 0.020*), although the total STAXI-2 S-Anger scores did not correlate with the severity of the spotting (ρ = 0.01, P = 0.946). TM taking contraceptives were not less likely to experience higher STAXI-2 S-Anger scores (P = 0.317). Serum testosterone levels were positively correlated with virilisation (ρ = 0.15, P = 0.008*) and negatively correlated with persistence of menstruation (ρ = −0.16, P = 0.032*). TM with a MINI-Plus diagnosis at baseline did not present with higher STAXI-2 S-Anger scores after 3 months of follow-up (data not shown).

In TW, total STAXI-2 S-Anger scores did not correlate with serum testosterone levels (ρ = 0.15, P = 0.017, independent of type of oestrogen therapy, P-values range: 0.008–0.795, or type of anti-androgen therapy, P-values range: 0.200–0.789 or type of anti-androgen therapy, P-values range:) or age (P = 0.079) and were independent of mode of oestrogen administration (P = 0.652), but they were correlated with PANAS negative affect scores (ρ = −0.57, P < 0.001*) and baseline poor social quality of life scores (ρ = 0.22, P = 0.004*). STAXI-2 S-Anger scores also correlated with baseline scores for the total SCL-90R score (ρ = 0.33, P < 0.001*) and SCL-90R factors somatization (ρ = 0.28, P < 0.001*), sleeping problems (ρ = 0.28, P < 0.001*), paranoid ideation/psychoticism (ρ = 0.31, P < 0.001*), hostility (ρ = 0.33, P < 0.001*), depression (ρ = 0.27, P < 0.001*) and interpersonal sensitivity (ρ = 0.26, P < 0.001*). TW with a MINI-Plus diagnosis at baseline did not present with higher STAXI-2 S-Anger scores after three months of follow-up. After partially controlling for PANAS negative affect scores, social quality of life, total SCL-90R scores and SCL-90R scores for the factors somatization, sleeping problems, paranoid ideation/psychoticism, hostility, depression and interpersonal sensitivity, there was no correlation between serum testosterone levels and total STAXI-2 S-Anger scores (P = 0.505).

3.1.2. Cross-sectional data: 12 months of follow-up

At the 12-month follow-up visit, there was no correlation between serum testosterone and total STAXI-2 S-Anger scores in TM (ρ = −0.04, P = 0.599, independent of type of testosterone therapy, P-values range: 0.129–0.405) or TW (ρ = 0.07, P = 0.313, independent of type of oestrogen therapy, P-values range: 0.137–0.851, or type of anti-androgen therapy, P-values range: 0.425–0.778). In both groups, there was a positive correlation between total STAXI-2 S-Anger scores and PANAS negative affect scores (TM: ρ = 0.43, P < 0.001*, TW: ρ = −0.60, P < 0.001*). Additionally, the presence of the SCL-90R factor somatization at baseline predisposed to higher cross-sectional STAXI-2 S-Anger scores at the 12-month follow-up visit (TM: ρ = 0.27, P < 0.001*, TW: ρ = 0.24, P = 0.002*) (Table 3). Total STAXI-2 S-Anger scores were independent of mode of androgen (P = 0.55) or oestrogen (P = 0.59) administration and independent of experiencing spotting (P = 0.055) or menstruation (P = 0.945). TM taking contraceptives were not less likely to experience higher STAXI-2 S-Anger scores (P = 0.370). The presence of a MINI-Plus diagnosis at baseline did not predispose to higher STAXI-2 S-Anger scores after 12 months of follow-up (data not shown). After partially controlling for PANAS negative affect scores and SCL-90R scores for the factors somatization, there was no correlation between serum testosterone levels and total STAXI-2 S-Anger scores in both TM (P = 0.330) and TW (P = 0.953).

3.1.3. Cross-sectional data: 36 months of follow-up

There was no correlation between total serum testosterone levels and total STAXI-2 S-Anger scores at the 36-month follow-up in either TM (ρ = −0.44, P = 0.280) or TW (ρ = 0.40, P = 0.082). In TW (but not in TM), there was a positive correlation between total STAXI-2 S-Anger scores and PANAS negative affect scores (ρ = 0.54, P = 0.001*). (Table 3) Age was not correlated with cross-sectional total STAXI-2 S-Anger scores at 36 months (TM: ρ = −0.33, P = 0.182, TW: ρ = 0.22, P = 0.201). Mode of oestrogen administration did not influence total STAXI-2 S-Anger scores (P = 0.739). The presence of a MINI-Plus diagnosis at baseline did not predispose to higher STAXI-2 S-Anger scores after 36 months of follow-up (data not shown). After partially controlling for PANAS negative affect scores, there was no correlation between serum testosterone levels and total STAXI-2 S-Anger scores in both TM (P = 0.035) and TW (P = 0.596).

3.2. Prospective data

As shown in Fig. 2, there was a trend towards an increase in total STAXI-2 S-Anger scores after three months of testosterone therapy in TM, compared to baseline (+0.90, 95%CI 0.04–1.75, P = 0.041). After one year, STAXI-2 S-Anger scores decreased back to baseline (−1.267, 95% CI −2.09 to −0.45, P = 0.185), after which they remained stable (Table 3, Fig. 2). There were no prospective changes in total STAXI-2 S-Anger scores in TW, as shown in Table 3.

3.2.1. Prospective data: 3 months of follow-up

Given the trend towards an increase in total STAXI-2 S-Anger scores during the first three months of testosterone therapy in TM (non-significant), prospective STAXI-2 S-Anger scores were tested for correlations with serum sex steroid levels, psychosocial measurements and clinical features including virilisation, spotting and menstruation. (Table 3) In addition, we assessed whether TM with diagnoses based on the MINI-Plus were more likely to present with a higher increase in STAXI-2 S-Anger scores during the first three months. TM with a higher increase in anger intensity over the first three months of follow-up did not show a larger increase in serum testosterone (ρ = −0.08, P = 0.227, independent of type of testosterone therapy, P-values range: 0.343–0.480). (Table 3) Age did not correlate with prospective STAXI-2 S-Anger scores (ρ = −0.01, P = 0.952). Prospective STAXI-2 S-Anger scores were independent of mode of androgen administration (P = 0.283). There was no difference in prospective total STAXI-2 S-Anger scores over three months in TM with versus without spotting (P = 0.164) or menstruation (P = 0.202). Prospective STAXI-2 S-Anger scores did not correlate to prospective virilisation scores (ρ = 0.12, P = 0.131) or prospective differences in the severity of spotting (ρ = −0.09, P = 0.32) or menstruation (ρ = −0.13, P = 0.125). TM not taking contraceptives were not less likely to experience a higher prospective increase in STAXI-2 S-Anger scores (P = 0.467). A larger increase in serum testosterone led to a lower intensity of spotting (ρ = −0.20, P = 0.005*), but not to a change in menstruation (ρ = 0.03, P = 0.649) or virilisation scores (ρ = 0.08, P = 0.192). However, larger prospective increases in serum testosterone during the first three months were positively correlated with higher cross-sectional scores for virilisation after three months (ρ = 0.15, P = 0.011*).

In addition, prospective scores for anger intensity were positively correlated with prospective scores for negative affect in TM (ρ = 0.40, P < 0.001*). Prospective STAXI-2 S-Anger scores were independent of mode of androgen administration (P = 0.358). People with a psychiatric diagnosis based on the MINI-Plus did not show a larger increase in prospective scores for anger intensity (data not shown). Measurements that did not significantly influence prospective STAXI-2 scores are shown in Table 3 (Table 3).

In TW, prospective scores for anger intensity did not correlate to prospective serum testosterone levels (ρ = −0.06, P = 0.402, independent of type of oestrogen therapy, P-values range: 0.294–0.720, or type of anti-androgen therapy, P-values range: 0.083–0.310) nor age (ρ = 0.04, P = 0.497). However, they were positively correlated with prospective scores for negative affect (ρ = 0.31, P < 0.001*). There was no correlation between prospective anger intensity scores and baseline psychological measures in TW (Table 3). After partially controlling for PANAS negative affect scores, there was no correlation between prospective serum testosterone levels and prospective total STAXI-2 S-Anger scores after three months in both TM (P = 0.673) and TW (P = 0.412).

Table 3
Correlations between prospective scores for anger proneness during the first 3, 12 and 36 months of follow-up (Δ total STAXI-2 S-Anger scores) and prospective levels of sex steroids, prospective virilization scores (Ferriman-Gallwey), prospective changes in menstruation and spotting, prospective levels of positive and negative affect and baseline psychological evaluation (UGDS, QOL, SCL-90R, BIS). Correlations were tested using Spearman's correlation coefficient. Significant correlations are indicated in bold (P-value). Correlations that remained significant after Bonferroni-Holm correction are indicated with *. (TM = transgender men, TW = transgender women, LH = luteinizing hormone, FSH = follicle stimulating hormone, SHBG = sex steroid binding hormone, UGDS = Utrecht Gender Dysphoria Scale, QOL = quality of life, SCL-90R = SCL-90R Symptom Checklist, BIS = Body Image Scale).

1. Prospective correlations with Δ total STAXI-2 scores

	TM			TW		
	3 months	12 months	36 months	3 months	12 months	36 months
Δ serum testosterone levels	P = -0.08	ρ = **0.15**	ρ = 0.45	ρ = −0.06	ρ = −0.01	ρ = −0.29
	P = 0.527	**P = 0.049**	P = 0.317	P = 0.402	P = 0.864	P = 0.275
Δ serum oestradiol levels	ρ = −0.02	ρ = −0.07	ρ = 0.67	P = 0.02	P = 0.03	ρ = −0.29
	P = 0.732	P = 0.390	P = 0.101	P = 0.746	P = 0.644	P = 0.275
Δ serum LH levels	ρ = 0.11	ρ = 0.01	ρ = −0.54	ρ = −0.08	ρ = 0.07	ρ = −0.09
	P = 0.118	P = 0.912	P = 0.216	P = 0.236	P = 0.381	P = 0.733
Δ serum FSH levels	ρ = 0.16	ρ = −0.10	ρ = −0.27	ρ = 0.03	ρ = 0.03	ρ = 0.01
	P = 0.477	P = 0.435	P = 0.562	P = 0.909	P = 0.831	P = 0.991
Δ serum SHBG levels	P = 0.13	ρ = −0.10	ρ = **−0.80**	ρ = −0.06	ρ = **0.29**	ρ = 0.33
	P = 0.249	P = 0.445	**P = 0.030**	P = 0.616	**P = 0.011**	P = 0.206
Δ Ferriman-Gallwey	ρ = 0.12	/	/	/	/	/
	P = 0.131					
Δ Menstruation	ρ = −0.13	/	/	/	/	/
	P = 0.125					
Δ Spotting	ρ = −0.09	/	/	/	/	/
	P = 0.317					
Δ PANAS positive affect	ρ = −-0.07	ρ = −0.01	ρ = **−0.57**	ρ = 0.02	ρ = −0.01	ρ = 0.12
	P = 0.267	P = 0.866	**P = 0.028**	P = 0.760	P = 0.837	P = 0.576
Δ PANAS negative affect	ρ = **0.40**	ρ = **−0.55**	ρ = 0.62	ρ = **0.31**	ρ = **−0.57**	ρ = **0.46**
	P < 0.001*	**P < 0.001***	P = 0.013	**P < 0.001***	**P < 0.001***	**P = 0.022**
Baseline UGDS	ρ = −0.10	ρ = −0.07	ρ = −0.02	ρ = 0.52	ρ = −0.14	ρ = **0.50**
	P = 0.198	P = 0.431	P = 0.943	P = 0.126	P = 0.305	**P = 0.047**
Total baseline QOL	ρ = −0.08	ρ = −0.05	ρ = −0.45	ρ = −0.03	ρ = −0.01	ρ = −0.03
	P = 0.324	P = 0.453	P = 0.192	P = 0.759	P = 0.981	P = 0.907
Baseline social QOL	ρ = −0.09	ρ = −0.01	ρ = −0.61	ρ = −0.02	ρ = −0.05	ρ = −0.03
	P = 0.324	P = 0.881	P = 0.061	P = 0.836	P = 0.564	P = 0.925
Baseline SCL90-R	ρ = 0.06	ρ = 0.16	/	ρ = −0.11	ρ = **−0.25**	/
	P = 0.439	P = 0.137		P = 0.204	**P = 0.017**	
Baseline BIS	ρ = 015	ρ = −0.16	ρ = −0.56	ρ = 0.02	ρ = −0.13	ρ = 0.10
	P = 0.099	P = 0.072	P = 0.073	P = 0.835	P = 0.147	P = 0.724

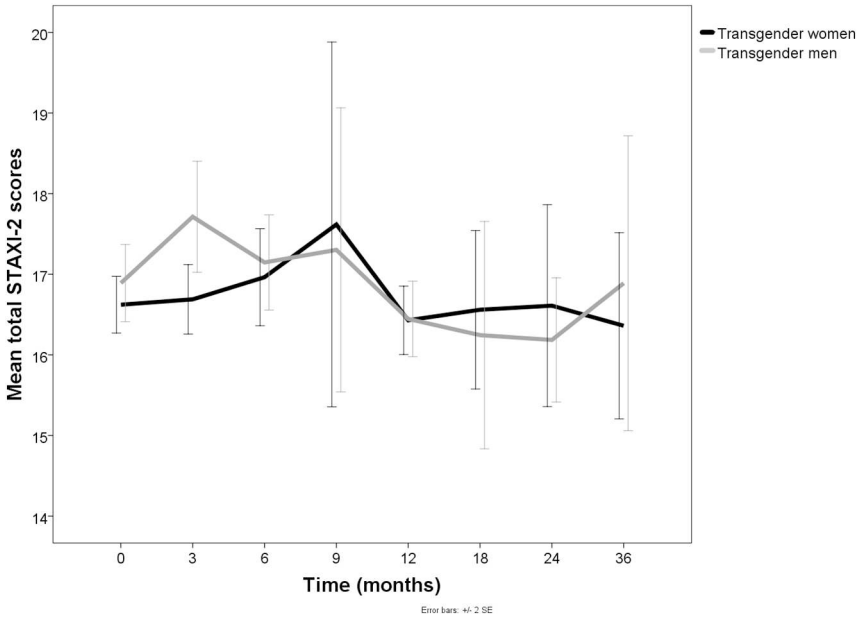

Fig. 2. Prospective STAXI-2 S-Anger scores over 36 months of follow-up in transgender men and transgender women.

3.2.2. Prospective data: 12 months of follow-up

Prospective scores for anger intensity were positively correlated with prospective scores for negative affect in both TM (ρ = 0.55, P < 0.001*) and TW (ρ = 0.56, P < 0.001*). After Bonferroni-Holm correction, there was no correlation between prospective serum testosterone levels and prospective scores for anger intensity in TM

(P = 0.049, independent of type of testosterone therapy, P-values range: 0.310–0.846) nor TW (P = 0.864, independent of type of oestrogen therapy, P-values range: 0.261–0.851, or type of anti-androgen therapy, P-values range: 0.258–0.842). Age was not correlated with prospective changes in total STAXI-2 S-Anger scores (TM: ρ = 0.01, P = 0.859, TW: ρ = −0.05, P = 0.462). Prospective STAXI-2 S-Anger scores were independent of mode of androgen (P = 0.145) or oestrogen (P = 0.325) administration. TM who still experienced spotting (P = 0.705) or menstruation (P = 0.155) were not more likely to show a higher prospective increase in STAXI-2 S-Anger scores. TM not taking contraceptives were not less likely to experience a higher prospective increase in STAXI-2 S-Anger scores (P = 0.366). People with a psychiatric diagnosis based on the MINI-Plus did not show a larger increase in prospective scores for anger intensity (data not shown). Measurements that did not significantly influence prospective STAXI-2 S-Anger scores are shown in Table 3 (Table 3). After partially controlling for PANAS negative affect scores, there was no correlation between prospective serum testosterone levels and prospective total STAXI-2 S-Anger scores after three months in both TM (P = 0.519) and TW (P = 0.588).

3.2.3. Prospective data: 36 months of follow-up

Prospectively over 36 months of follow up, anger intensity was not correlated with prospective serum total testosterone levels in TM (ρ = 0.46, P = 0.317) or TW (ρ = 0.29, P = 0.275). Age was not correlated with prospective changes in total STAXI-2 S-Anger scores (TM: ρ = −0.35, P = 0.190, TW: ρ = 0.22, P = 0.201). Measurements that did not significantly influence prospective STAXI-2 S-Anger scores are shown in Table 3.

4. Discussion

In the current literature, there is no consensus regarding the effect of endogenous and/or exogenous testosterone on aggression and aggressive behaviour (Book et al., 2001; Choi et al., 1990; Dabbs Jr et al., 1987; Ehrenkranz et al., 1974; Eisenegger et al., 2011; Gray et al., 1991; Kreuz and Rose, 1972; O'Connor et al., 2002; Pope and Katz, 1992; Tricker et al., 1996; Vermeersch et al., 2008) and previous research concluded that gender affirming hormone therapy does not contribute to aggression in transgender people (Defreyne et al., 2018). If angry feelings are externalized, they can lead to verbally or physically aggressive actions. However, angry feelings can also be internalized, which does not lead to aggression, but involves a state of tension, high energy and externalized blame and can be associated with adverse health outcomes, such as elevated blood pressure and cardiovascular problems (Spielberger, 1988). It remains unclarified whether anger experience and expression are related to gender (Kopper and Epperson, 1991; Thomas, 1993). Regarding the relationship between anger and testosterone therapy in TM, only two manuscripts have been published: Van Goozen et al. first observed an increase in anger 3 months after the initiation of gender affirming hormone treatment (Van Goozen et al., 1995). However, they did not test for correlations with serum testosterone levels. More recently, Motta et al. compared STAXI-2 scores of 52 TM with a control group at baseline and after the initiation of gender affirming hormonal therapy (Motta et al., 2018). They did not include TW, nor did they perform prospective analyses. The group concluded that there was an increase in anger expression in TM after 7 months of gender affirming hormone therapy, but this increase was not correlated with serum testosterone levels. The increase was however correlated with the persistence of menstrual bleeding and the presence of Axis I psychiatric disorders.

The present study shows that the initiation of gender affirming hormonal therapy did not cause an increase in state-level anger intensity in TM. Prospective and cross-sectional scores for state-level anger intensity were not correlated to serum testosterone levels, but were positively correlated to negative affect, total (TM) and social (TW) poor quality of life and SCL-90R factors including the total SCL-90R score, somatization, paranoid ideation/psychoticism, hostility, depression, anxiety, interpersonal sensitivity and sleeping problems (only in TW).

High Negative Affect is described as a state of subjective distress and unpleasurable engagement, with a variety of mood states that includes anger (Watson et al., 1988), therefore the two scales (PANAS and STAXI-2 S-Anger) are related to each other and persons presenting with higher anger intensity may be more likely to present with higher scores for negative affect.

A correlation between anger and psychopathology has been described in previous research, including Axis I disorders (mood disorders, psychotic disorders, eating disorders, anxiety disorders, dissociative disorders, substance use disorders), cluster B personality disorders (e.g. borderline personality), paranoid disorders, somatization, sleeping problems and hostility (Caska et al., 2009; Choi et al., 2001; Novaco, 2010; Troisi and D'Argenio, 2004). In addition, certain quality of life areas, such as low health-related quality of life, have been associated with anger (Dan et al., 2007; Julkunen and Ahlström, 2006).

Cisgender women diagnosed with polycystic ovarian syndrome (PCOS), a condition characterized by high serum testosterone levels, often report psychological distress caused by living with the symptoms of PCOS (Barry et al., 2018). These women also report more aggression (Elsenbruch et al., 2003), more anger symptoms and a greater tendency to withhold anger (Barry et al., 2011). In cisgender women with PCOS, endogenous testosterone was not correlated with mood states (including aggression), but the impact of the PCOS symptoms on quality of life could partly explain the observed mood disturbance (Barry et al., 2018). We hypothesize that, as gender dysphoria decreases in TM after the initiation of testosterone therapy (of which the impact on anger and aggression is uncertain), quality of life will increase, which is correlated with a decrease in state-level anger intensity (Barry et al., 2011; Dan et al., 2007; Julkunen and Ahlström, 2006).

In the current study sample, people with higher scores on SCL-90R factors and lower quality of life presented with higher state-level anger intensity at all follow-up visits. People with a psychological and/or psychiatric vulnerability before the initiation of gender affirming hormone treatment did not show a larger increase in state-level anger intensity during follow-up, compared to persons without psychological and/or psychiatric vulnerability. Therefore, we conclude that gender affirming hormone therapy does not increase state-level anger intensity in transgender people, independent of any co-occurring psychiatric disorders.

TM who still experienced spotting after three months of gender-affirming hormone therapy presented with higher scores for state-level anger intensity, which is in line with Motta et al., who described higher anger expression in TM with persistent menstrual bleedings or Axis I disorders, without a correlation with circulating testosterone levels (Motta et al., 2018). Spotting can lead to increased psychological distress in TM because this can be perceived as a reminder of the undesired sex (Armuand et al., 2017; Mitu, 2016). Therefore, it is important to ask TM if suppression of the menstrual cycle is desired and to initiate progestin or GnRH agonist therapy, if required, as is also suggested by the SOC7 (WPATH, 2012) and the endocrine society guidelines (Hembree et al., 2017).

Our study results may have been affected by several limitations. In some patients, the STAXI-2 S-Anger questionnaire was not assessed at all visits and we did not assess T-Anger, anger expression or anger control. More information is needed regarding the effects of gender affirming hormone therapy on transgender people's disposition to experience anger as a personality trait and their expression and ability to control their anger. Follow-up in Amsterdam only took place during the first year of gender affirming hormonal treatment, leading to a decrease in sample size and power in the analyses of the 18th, 24th and 36th month. The study is also limited by the tool used to measure anger intensity; the STAXI-2 questionnaire S-Anger, which is a patient

reported outcome measure (PROM), having the disadvantage that the obtained data are subjective. In the current sample, there was only a slight variation in reported total STAXI-2 S-Anger scores, with the majority of the transgender people reporting virtually no current angry emotions, which may be due to social desirability. The STAXI-2 S-Anger questionnaire assesses anger intensity at the current moment, without asking about certain situations in which anger or aggression are provoked. Unfortunately, we did not prospectively assess the questionnaires used in the baseline psychological battery, nor did we collect data on violent behaviour or self-harm or harm of others. In addition, blood samples were obtained at fixed time points during the follow-up period, independent of the time interval to the last testosterone administration. This may have led to fluctuations in measured serum testosterone and oestradiol levels. Unfortunately, time interval to the last testosterone administration was not recorded.

Despite these limitations, this study has several strengths. To our knowledge, this is the largest prospective study to date in which anger in both TM and TW was evaluated and correlated cross-sectionally as well as prospectively to serum levels of sex steroids. Our study cohorts are well defined and participants adhered to a strict treatment regimen.

5. Conclusions

Evidence from a prospective study did not show a correlation between state-level anger intensity and exogenous testosterone administration in TM or oestrogen plus anti-androgen therapy in TW. Persons with a higher increase in serum testosterone levels did not have a higher increase in state-level anger intensity over time, nor did persons with higher cross-sectional serum testosterone levels present with higher scores for state-level anger intensity. However, there appeared to be a trend towards a positive correlation between serum testosterone levels and anger after three months of gender affirming hormone therapy in both TM and TW. The current study indicates that gender affirming testosterone treatment does not affect state-level anger intensity in TM nor TW, although future research on anger and aggression in transgender people receiving gender affirming hormone therapy should focus preferentially on short term (0–3 months) data.

TM with lower serum testosterone levels after three months were more likely to have persistent menstruation. Persistent menstrual spotting resulted in higher state-level anger intensity. We suggest adding a progestin or a GnRH analogue to the treatment regimen if the presence of menstruation/spotting is distressing.

In addition, TM and TW with psychological and/or psychiatric vulnerability and/or higher negative affect were more likely to experience higher state-level anger intensity, but they did not experience an increase in state-level anger intensity after the initiation of gender affirming hormone therapy. Therefore, we conclude that gender affirming hormone therapy can safely be initiated in transgender people with psychological and/or psychiatric vulnerability.

Funding

This work was funded by an ESSM (European Society for Sexual Medicine) grant, grant number RG17-19.

Declarations of interest

None.

Acknowledgements

We would like to thank the following persons for their valuable contributions in the ENIGI project: Alessandra D Fisher, Thomas Schreiner, Inga Becker and Timo Nieder for participating as a center in the ENIGI project, the endocrinology residents (Chantal Wiepjes, Nienke Nota, Maartje Klaver, Christel De Blok, Greet Roef, Mirra Boer, Marijn Carpentier, Liesbeth Van Huffel, Sara Vandewalle, Loes Moernaut, Sabine Vermeersch, Xavier-Philippe Aers, Gert-Jan Vereecke, Charlotte Verroken and Emmanuelle Versele) for their outpatient care, Sean Iwamoto for reviewing the manuscript for grammatical errors, Charlotte Bultynck, Charlotte Pas, Anne-Sophie De Maetelaere and Kessewa Abosi-Appeadu for their help with the dataset and our study nurse, Kaatje Toye, for handling the extensive administration to the study. We also wish to thank all participants in the ENIGI study protocol.

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