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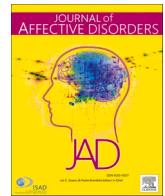
Research paper

Changes in depression symptom profile with gender-affirming hormone use in transgender persons

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ABSTRACT

Background: Women show higher prevalence of depression and different symptomatology than men, possibly influenced by sex hormones. Many transgender persons, who face a high risk of depression, use Gender-Affirming Hormone Therapy (GAHT), but the impact of GAHT on depressive symptom profiles is unknown.
Methods: This study examined depressive symptoms in transgender persons before GAHT and after 3- and 12 months of GAHT. We used the Inventory of Depressive Symptomatology-Self Report to assess depressive symptoms, exploratory factor analysis (EFA) to assess symptom clusters, and linear mixed models to assess changes in symptom clusters.
Results: This study included 110 transmasculine (TM) and 89 transfeminine (TF) participants. EFA revealed four symptom clusters: mood, anxiety, lethargy, and somatic symptoms. Changes in total depressive symptoms significantly differed between TM and TF groups. After 3 months of GAHT, TM participants reported improvement in lethargy (-16%; 95%CI: -29%; -2%), and after 12 months TF participants reported worsening in low mood (24%; 95%CI: 3%; 51%), but absolute score changes were modest. Neither group showed changes in anxiety or somatic symptoms.
Limitations: This study had limited sample sizes at 12 months follow-up and did not include relevant biological or psychosocial covariates.
Discussion: Changes in depressive symptoms after GAHT use differ in TM and TF persons: TM persons report slight improvements in lethargy, whereas TF persons report a slight increase in low mood. Starting GAHT represents a significant life event with profound social and physical effects, and further research should assess social and biological effects of GAHT on mood-related symptoms.

1. Introduction

There is a known sex difference in depression: cisgender women are twice as likely to experience depression in their lifetime compared to cisgender men (Kuehner, 2003). There are indications that biological factors underlie this increased risk of depression in women. Recent advances in the field of reproductive psychiatry point to a possible role of sex hormones in the risk of mood disorders (Schweizer-Schubert et al., 2021), as illustrated in the female lifespan, in which the risk of depression increases in life phases when female sex hormones fluctuate,

such as pregnancy and perimenopause (Soares and Zitek, 2008). Furthermore, cisgender females also show mood changes after exogenous hormone interventions (Eisenlohr-Moul et al., 2023; Frokjaer, 2020).

The clinical symptomatology of depression also seems to differ between cisgender men and women. Cisgender women show higher prevalence and severity of symptoms of "atypical depression" (e.g. more weight gain, increased appetite, hypersomnia, and interpersonal sensitivity) while cisgender men report more symptoms of melancholic depression, such as severe anhedonia and low mood (Khan et al., 2006), and more psychomotor agitation (Marcus et al., 2005; Schuch et al., 2014).

Data-driven analyses have provided insight into symptom profiles of depression: using analyses such as Exploratory Factor Analysis (EFA), researchers have identified underlying dimensions of depressive symptoms. These symptom dimensions, also called clusters, can also be used as questionnaire subscales. Previous studies showed population differences between symptom clusters: EFA in a clinically depressed population showed four symptom clusters for mood-, anxiety-, somatic- and sleep-related symptoms (Wardenaar et al., 2010), whereas, for instance, EFA in an elderly cohort has shown three symptom clusters for mood, motivation, and somatic symptoms (Hegeman et al., 2012).

A subpopulation for whom the effect of sex hormones on depression is especially relevant is the transgender population. Transgender persons' gender identity is not in line with their sex assigned at birth, which can result in gender dysphoria. Gender-affirming hormone therapy (GAHT) can reduce this incongruence between gender identity and physical features: transmasculine (TM) persons, who were assigned female at birth but want to masculinize their bodies, can use testosterone, and transfeminine (TF) persons, who were assigned male at birth but want to feminize their bodies, can use estradiol and anti-androgens. Although studies generally find a positive effect of GAHT on depression prevalence, the effects of GAHT on the symptom profile of depression are yet unknown.

Based on the findings in cisgender persons, it is important to assess whether sex hormones can also change the symptom profiles of depression (i.e. which symptoms or clusters of symptoms change after GAHT) in transgender persons. Prevalence rates for depression in transgender persons, before accessing gender-affirming care, range from 42 % to 48 % (Aldridge et al., 2021; Colizzi et al., 2014), compared to 8.5 % in the cisgender population (Ten Have et al., 2023). One explanation for this improvement is the effects of GAHT on psychosocial well-being, which include improved body image (van de Grift et al., 2017), improved self-esteem (Gorin-Lazard et al., 2012), reduced social distress (Gómez-Gil et al., 2012) and improved quality of life (van Leerdam et al., 2021; White Hughto and Reisner, 2016). However, the prevalence of severe depressive symptoms in the first years of GAHT is still relatively high: respectively, 23 % and 26 % of transgender persons experience significant symptoms of depression after 12 and 18 months of GAHT (Aldridge et al., 2021; Colizzi et al., 2014).

Other studies find that masculinizing and feminizing hormones have different impacts on mood: Masculinizing GAHT could flatten positive and negative mood, whereas findings are mixed for effects of feminizing GAHT on mood (Matthys et al., 2021; Slabbekoorn et al., 2001; Wierckx et al., 2012). It is also possible that feminizing and masculinizing hormones have different effects on neurobiology. Use of masculinizing GAHT was associated with increased binding to serotonin reuptake transporter (SERT; Kranz et al., 2015), downregulation of monoamine oxidase A (MAO-A; Kranz et al., 2021), and changes in brain metabolites (Collet et al., 2023a). Use of feminizing hormones was associated with decreased binding to SERT (Kranz et al., 2015), but no changes in downregulation of MAO-A (Kranz et al., 2021). It is possible that these changes could also result in in differing effects of masculinizing or feminizing GAHT on depressive symptoms.

This study aimed to address symptom profiles of depression in transgender persons and the influence of GAHT. The first aim was to examine depression symptom profile just before the start of GAHT and to compare the profiles between TM and TF persons. The second aim was to study the effect of GAHT, by studying the changes in symptom profiles after 3 and 12 months of GAHT, and assessing whether these significantly differ between TM and TF participants.

Based on population differences in cisgender populations, we hypothesize that before GAHT, the TM group will report more symptoms of atypical depression (e.g. increase in appetite and weight, higher interpersonal sensitivity, and hypersomnia) and that the TF group will report more severe anhedonia and low mood. After starting GAHT, we hypothesize that the severity of depressive symptoms will decrease in both groups due to psychosocial effects of GAHT, but that, the TM group will show a stronger decrease in overall depressive symptoms and a stronger decrease in atypical symptoms than the TF group due to biological effects of GAHT.

2. Methods

2.1. Study setting

We used data from two studies: the European Network for the Investigation of Gender Incongruence (ENIGI) study and the Relationship between Emotions and Sleep in Transgender persons: Endocrinology and Depression (RESTED) study. The ENIGI-endocrinology study is a multi-center cohort study that examines the effects of GAHT (Dekker et al., 2016), conducted at five treatment centers (Ghent, Florence, Tel Aviv, Oslo, and Amsterdam). Because of logistical reasons, the ENIGI data for this study was only collected in Amsterdam at the Amsterdam University Medical Center (Amsterdam UMC, location VU medical center) from January 2020 to July 2022. The RESTED study aims to study changes in sleep architecture, insomnia, and depression after GAHT. It is a multi-center study involving Amsterdam UMC and University Medical Center Groningen (UMCG). The RESTED data for this study were collected between January 2020 and August 2022. Both studies received a declaration from the Medical Ethics Review Committee of the VU medical center stating that Medical Research Involving Human Subjects Act (WMO) did not apply to the studies (ENIGI: study id. 2019.469 and RESTED: study id. 2019.353). For the RESTED study, approval for participation was obtained by the local ethical committee of the UMCG. All participants provided informed consent.

2.2. Participants

Participants in both studies were included if they were going to start GAHT at one of the participating centers if they could speak, read and write Dutch, and if they were 18 years or older. For the RESTED study, participants were not included if they had used GAHT before, if they had been diagnosed with sleep disorders, were using benzodiazepines or opiates, or if they were aged over 50 years. Since previous use of GAHT was not an exclusion criterion for participation in the ENIGI cohort study, we excluded ENIGI participants who were not hormone-naïve (e.g. had previously used GAHT or were already using GAHT; $n = 7$) from the current study database.

The baseline sample of ENIGI in this study was $n = 198$, and the baseline sample of the RESTED cohort was $n = 97$. Participants could participate in both studies, as displayed in Fig. 1. If individuals participated in both studies, duplicate measurements were removed. Due to the ongoing character of both cohort studies and loss to follow-up, sample sizes differ at each measurement time point.

2.3. Gender-affirming hormone therapy

To accurately reflect the grouping of participants, as recommended by Peters et al. (2023), we split the participant groups by GAHT formulations.

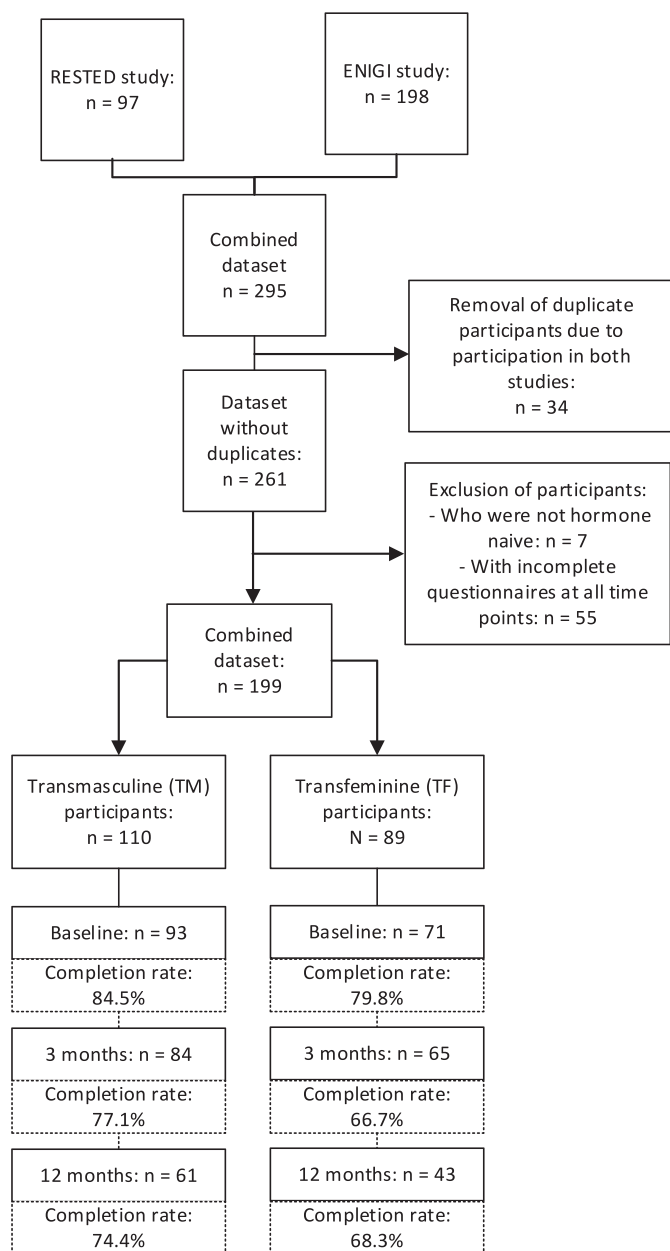Masculinizing hormones for TM participants were administered in

Fig. 1. Inclusion flowchart of study participants and measurements in the current study, including completion rates at each follow-up measurement. Due to the prospective character of the studies, sample sizes are smaller at follow-up: completion rates show the percentage of participants who reached follow-up and completed the measurement questionnaire at that time point. All participants included in the final dataset contributed a complete IDS-SR to at least one time point.

the form of transdermal testosterone (daily dose of 40.5 mg) or intramuscular testosterone (short-acting testosterone esters, 250 mg every 3 weeks, or long-acting testosterone undecanoate, 1000 mg every 12 weeks). TM participants could also use progestins or combined hormonal contraceptives to suppress menstrual cycles. It should be noted that in the participating centers, gonadotropin-releasing hormone (GnRH) analogs were not used to suppress endogenous hormone production in the TM group.

Feminizing hormones for TF participants consisted of oral estradiol (estradiol valerate, 2 mg twice daily) or transdermal estradiol (estradiol patches, 100 μg per 24 h, twice a week; estradiol spray, 4.59 mg daily; estradiol gel 0.06 %, 1.5 mg daily) combined with an anti-androgen,

either cyproterone acetate (daily dose of 10 mg) or GnRH-analogs, (triptorelin, 3.75 mg per 4 weeks; triptorelin, 11.25 mg per 12 weeks). Several TF participants only used estradiol or anti-androgens. Sensitivity analyses were conducted to compare results between TF participants using both and TF participants using only estradiol or only anti-androgens (i.e. "incomplete GAHT"), of which results are reported in Supplementary Table 1.

2.4. Variables

2.4.1. Demographic and clinical variables

Participants' age (range 16 to 68, interquartile range from 21 to 29), sex assigned at birth, previous hormone use, and current medication were recorded at outpatient clinic visits by participants' healthcare providers. Gender identity was inquired in a questionnaire in the study survey (in the ENIGI study) or obtained from medical files based on reported gender identity at the time of starting GAHT (in the RESTED study). To assess psychiatric comorbidities, the Mini-International Neuropsychiatric Interview (MINI+; Sheehan et al., 1998) was conducted shortly after clinical entry in all participants from the Amsterdam UMC, but not in participants from the UMCG. If participants had their clinic intake under the age of 18, the MINI+ interview was not conducted, since an age-appropriate instrument was used to assess psychiatric conditions. Demographic characteristics were not added to the main analyses, but analyses incorporating age, study, cycle regulation use, testosterone form and estrogen form are reported in Supplementary Table 2.

2.4.2. Depressive symptoms

Both studies used a digital survey program to send out invitation links to the questionnaires, which were sent to participants in the weeks or months before the start of GAHT (in the RESTED study) or at the start of GAHT (in the ENIGI study) and after 3 and 12 months of GAHT. Surveys were only saved in the research environment and were not accessible to participants' healthcare providers to ensure maximum anonymity for study participants.

The Dutch version of the 30-item Inventory of Depressive Symptomatology-Self Report (IDS-SR; Rush et al., 1996) was used to assess depressive symptoms. It inquires about depressive symptoms in the last seven days, with items ranging from 0 to 3 (0 = lowest severity, 3 = highest severity). In line with the standardized scoring, items 11 and 12 and items 13 and 14 were rescored into two items ("change in appetite" and "change in weight", respectively), resulting in a 28-item total (range 0 to 84). Cutoff scores for the IDS-SR indicate no depression (≤ 13 points), mild (14 to 25 points), moderate (26 to 38 points), severe (39 to 48 points), and very severe depressive symptoms (≥ 49 points) (Rush et al., 1996). The IDS-SR has adequate internal consistency in the cisgender population (Cronbach's alpha = 0.88; Rush et al., 1996).

2.5. Statistical methods

2.5.1. Data cleaning

All statistical analyses were conducted in Rstudio (version 1.3.1093). Participants' IDS-SR questionnaire was excluded if >10 % of items were missing. 19 measurements had 1 or 2 missing items (17 ENIGI study measurements and 2 RESTED study measurements). Imputation of these missing items was performed using the "mice" package for Rstudio (van Buuren and Groothuis-Oudshoorn, 2011).

2.5.2. Symptom clusters

To determine the symptom clusters of the IDS-SR at baseline, we used exploratory factor analysis (EFA) with maximum likelihood (ML) estimation. EFA analysis was conducted using the "psych" package (Revelle, 2017). To determine the number of factors to fit the data, we used parallel analysis, using Scree plot inspection combined with Kaiser's rule. Due to the high likelihood of between-item correlations, oblimin

rotation was used for extraction. Items with a loading of 0.4 or higher were included in each factor, and if items were loading on two factors they were included in the factor with the highest loading. Four EFA models were fit with solutions for 2, 3, 4, and 5 factors. Model fit was interpreted using Tucker Lewis Indices (TLI), Root Mean Square Error of Approximation (RMSEA), and these measures are also reported in Supplementary Materials 3. The symptom clusters were used as subscales of the IDS-SR in subsequent analyses.

2.5.3. Longitudinal course of symptoms

Since all models violated the assumption of normally distributed residuals, the IDS-SR score and subscales were log-transformed (i.e. log $(Y + 1)$). All estimated changes have therefore been reported as estimated percentages of change. To analyze changes in the IDS-SR total score and the subscales derived from the clusters as found in the EFA analyses, we used linear mixed models with the lme4 package (Bates et al., 2015) and lmerTest package (Kuznetsova et al., 2017) in Rstudio.

For all analyses addressing baseline measurements (i.e. EFA analyses and comparison of IDS-SR scores and subscores between the TM and TF groups at baseline) we used the full baseline sample. Linear regression was used to assess differences in baseline scores between TM and TF groups.

Longitudinal analyses comparing baseline to follow-ups (i.e. examination of changes in IDS-SR scores and subscores after 3 or 12 months of GAHT) were conducted in participants who contributed both a baseline and at least one follow-up measurement. Linear mixed models were used to assess changes in the IDS-SR scores and cluster scores after 3 and 12 months of GAHT. The linear mixed models assessing changes over time included time point as categorical fixed predictor, participants' baseline score as fixed predictor, and a random intercept per participant. Differences between the TM and TF group over time were studied by adding an interaction term to the aforementioned model. Analysis outcomes were reported using medians of the scores as well as the estimated change resulting from the linear mixed models. The full model specifications are also reported in Supplementary Table 3.

3. Results

3.1. Participant demographics

The total participant sample included 199 participants, of whom 164 completed the IDS-SR at baseline, 148 at 3 months of GAHT and 105 at 12 months of GAHT. In the full cohort (i.e. $n = 199$), participants' median age was 24 years (IQR: 21 to 29) old, and 13.1 % used psychotropic medication. Of all participants, 73.9 % of the participants reported a binary gender identity (i.e. (transgender) man or (transgender) woman), 12.1 % reported a non-binary gender identity (i.e. a gender identity outside of the binary gender identity options) and for 13.6 % gender identity was missing. Data from MINI+ assessments indicate that at clinical intake, 47.2 % of the participants had a lifetime diagnosis of depression or dysthymia. Participant demographics and clinical characteristics are also displayed in Table 1.

3.1.1. Depressive symptom severity at baseline and after GAHT

At the start of GAHT, 22.4 % of participants ($n = 19$) exhibited moderate, severe, or very severe depressive symptoms based on IDS-SR scores. In the TM group, 26 % of participants ($n = 14$) reported depressive symptoms of this severity and in the TF group, 16.1 % of participants ($n = 5$) reported symptoms of this severity. Following 12 months of GAHT, 16.5 % of participants ($n = 14$) still had moderate, severe, or very severe depression. 26 % of TM participants ($n = 14$) and 2.3 % of TF participants ($n = 5$) displayed depressive symptoms of this severity after 12 months of GAHT. Fig. 2 shows a breakdown of IDS-SR categories for each group and time point.

Table 1
Clinical and demographic baseline characteristics of study participants.

		Transmasculine group	Transfeminine group
Sample size in total cohort		110	89
Age	Median (IQR)	22 (20 to 26)	26 (23 to 33)
Gender identity (n, %)	Binary[a]	77 (70.0 %)	70 (78.6 %)
	Non-binary[a]	19 (17.3 %)	5 (5.6 %)
	Don't know	1 (0.9 %)	0 (0 %)
	Missing	13 (11.8 %)	14 (15.7 %)
Current or lifetime MINI+ psychiatric diagnoses (n, %)	Any comorbidity	55 (50.0 %)	49 (55.1 %)
	Depression or dysthymia	52 (47.3 %)	42 (47.2 %)
	Generalized Anxiety Disorder	4 (3.6 %)	2 (2.2 %)
	Social phobia or agoraphobia	13 (11.8 %)	12 (13.5 %)
	Posttraumatic Stress Disorder	5 (4.5 %)	1 (1.1 %)
	ADHD	4 (3.6 %)	3 (3.4 %)
	Missing[b]	27 (24.5 %)	16 (18.0 %)
Alcohol (median, interquartile range)	Consumptions per week	0.25 (0 to 1)	0.4 (0 to 2)
	Missing	17 (15.5 %)	15 (16.9 %)
Drug use (n, %)	No drug use	96 (87.3 %)	76 (85.4 %)
	Drug use	11 (10.0 %)	5 (5.6 %)
	Missing	3 (2.7 %)	8 (9.0 %)
Smoking (n, %)	Never	75 (68.2 %)	63 (70.8 %)
	Previous	14 (12.7 %)	6 (6.7 %)
	Current	16 (14.5 %)	13 (14.6 %)
	Missing	5 (4.5 %)	9 (10.1 %)
Psychotropic medication use (n, %)	Any psychotropic medication	16 (14.5 %)	10 (11.2 %)
	Antidepressants	9 (8.2 %)	5 (5.6 %)
	Anxiolytics	3 (2.7 %)	0 (0 %)
	Stimulants	4 (3.6 %)	6 (6.7 %)
	Antipsychotics	4 (3.6 %)	2 (2.2 %)
	Mood stabilizers	1 (0.9 %)	0 (0 %)
Form of testosterone prescribed at start of GAHT (n, %)	Testosterone gel	92 (83.6 %)	–
	Testosterone esters	16 (14.5 %)	–
	Testosterone undecanoate	2 (1.8 %)	–
Form of estrogen prescribed at start of GAHT (n, %)	Estradiol tablets	–	49 (55.0 %)
	Estradiol patches	–	28 (31.5 %)
	Estradiol gel	–	6 (6.7 %)
	Estradiol spray	–	3 (3.4 %)
	None[c]	–	3 (3.4 %)
Form of anti-androgens prescribed at start of GAHT (n, %)	Cyproterone acetate	–	17 (19.1 %)
	GnRH analogues	–	67 (75.3 %)
	None[c]	–	5 (5.6 %)

[a] Binary gender identity: identification as (transgender) man or woman; all participants who did not identify with these gender identities were grouped under non-binary gender identity.
[b] Missing MINI+ since the MINI+ interview was not conducted.
[c] Use of only estrogen or anti-androgens was categorized as incomplete GAHT use and studied in a sensitivity analysis.

3.2. Depression profile at the start of GAHT

3.2.1. EFA analysis

Analysis of baseline IDS-SR scores showed that the internal consistency of the IDS-SR in the total sample was good (Cronbach's alpha = 0.89). Results of the EFA analyses on the baseline measurements indicated that the 5-factor model showed the best fit, but this model had one factor with only one item with a loading over 0.4. The next best model fit was seen in the 4-factor model (TLI = 0.92 and RMSEA = 0.043), which was therefore chosen for further analysis and is displayed in Supplementary Table 4. This model showed that items related to mood or affect loaded on the first factor ("Mood" factor), items related to anxiety or self-image loaded on the second factor ("Anxiety"), items related to lethargy loaded on the third factor ("Lethargy") and items related to
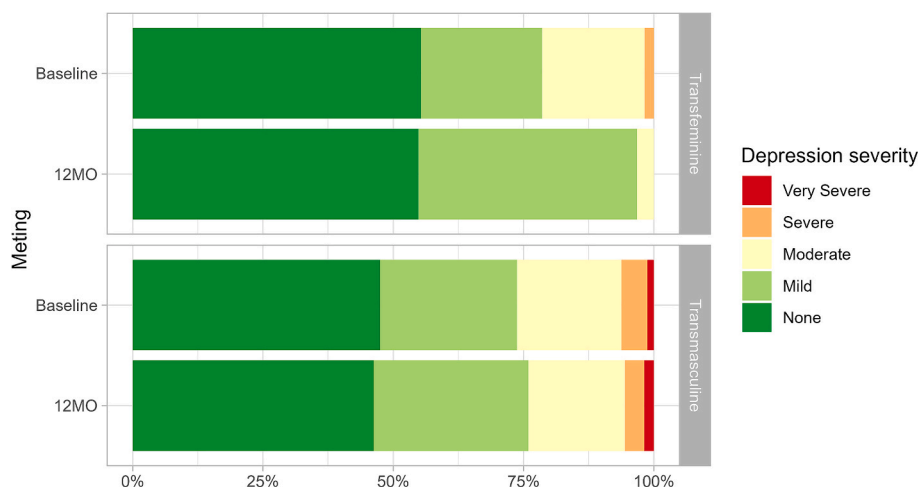
Fig. 2. Depression severity based on IDS-SR scores at baseline and after 12 months of GAHT. Prevalences are displayed per group at the start of GAHT and after 12 months of GAHT. Only participants with complete IDS-SR questionnaires at baseline and 12 months were included in the figure.

physical complaints loaded on the fourth factor ("Somatic"). A total of 12 items did not show loadings over 0.4 and were therefore not included in any of the factors. All factor loadings are shown in the Supplementary Table 4, and the symptom clusters and factor loadings are displayed in Fig. 3.

3.2.2. IDS total score and cluster scores at baseline

Baseline scores in the full cohort showed that at baseline, the TM group did not report higher total IDS-SR scores compared to the TF group (TM: median 15, IQR 9 to 28 versus TF: median 11, IQR 7 to 22.5; $p = 0.055$). At the start of GAHT, we found no significant differences in the subscale scores for mood (TM: median 2, IQR 0 to 4 versus TF: median 2, IQR 1 to 3; $p = 0.84$), anxiety (TM: median 2, IQR 0 to 5 versus TF: median 2, IQR 1 to 4; $p = 0.84$), lethargy (TM: median 3, IQR 1 to 5 versus TF: median 1, IQR 0 to 4; $p = 0.073$) or somatic symptoms (TM: median 1, IQR 0 to 1 versus TF: median 0, IQR 0 to 1; $p = 0.059$).

3.3. Depression profile changes after start of GAHT

3.3.1. Changes in IDS total score and cluster scores after GAHT

All longitudinal analyses were conducted on measurements from participants who contributed a baseline measurement and at least one follow-up measurement. Results show that the total IDS-SR score in the total cohort (i.e. TM and TF groups together) did not show any significant change after either 3 months or 12 months of GAHT. Interaction analyses comparing the groups shows that the TF group showed a significantly stronger increase in the total IDS-SR compared to the TM group after 3 months ($+25.1$ %, 95 % CI = 2.9 % to 52.0 %, $p = 0.026$) and 12 months ($+29.1$ %, 95 % CI = 2.9 % to 61.7 %, $p = 0.029$) of GAHT.

The cluster scores based on the symptom clusters found in the EFA analysis showed no significant changes after 3 or 12 months of GAHT in the total cohort (i.e. TM and TF groups together). In the TM group, the subscales for mood, anxiety, and somatic symptoms did not show significant changes after 3 or 12 months of GAHT. However, the TM group showed a significant decrease in lethargy symptoms (-16.3 %, 95 % CI: -28.5 % to -2.0 %, $p = 0.03$) after 3 months of GAHT, but no significant change after 12 months of GAHT compared to baseline. In the TF group, the total subscales for anxiety, lethargy, and somatic symptoms did not significantly change after 3 months or 12 months of GAHT. The TF group showed a significant increase in mood symptoms after 12 months of GAHT ($+24.3$ %, 95 % CI: 2.6 %; 50.6 %, p = 0.03) compared to baseline. It must be noted that although the subscores in lethargy and mood in the TM and TF groups show changes after starting GAHT use, the medians of the subscores are and remain below 3 points during

GAHT use. Absolute scores per time point and full results of all longitudinal models are displayed in Table 2, and the estimated changes are displayed in Fig. 4.

3.3.2. Sensitivity analyses

Sensitivity analyses assessing the effects of only complete GAHT in the TF group, excluding users of incomplete GAHT (i.e. use of estradiol or anti-androgens, but not both), show similar estimates and effect sizes compared to analyses in the full sample, as reported in Supplementary Table 1. Sensitivity analyses adjusted for age, cohort, cycle regulation use, testosterone form (i.e. transdermal or injections) and estrogen form (i.e. transdermal or oral) also show similar estimates, as reported in Supplementary Table 2. Higher age was significantly associated with higher IDS-SR scores, but the addition of age did not change estimated outcomes for the total IDS-SR.

4. Discussion

This study aimed to assess the symptom profile of depression in transgender persons at the start of GAHT, and to assess possible changes in the symptom profile and severity during the first 12 months of GAHT. Depressive symptoms show four clusters: mood-, anxiety-, lethargy-, and somatic symptoms. After 3 and 12 months of GAHT use, the overall cohort reports no significant changes in total IDS-SR scores, nor in any of the subscales. TF participants show a significantly larger increase in the total IDS-SR scores compared to TM participants after 3- and 12 months of GAHT. The TM participants showed a modest but significant temporary decrease in lethargy-related symptoms after 3 months of GAHT. The TF participants showed a modest but significant increase in mood-related symptoms after 12 months of GAHT.

The clusters found in the EFA analyses differ from the clusters as originally found in the IDS-SR by Rush et al. (1996) and from clusters previously found in a cisgender Dutch population (Wardenaar et al., 2010), which showed clusters around mood and cognition, anxiety and somatic complaints and sleep. This may be due to specific adversities that transgender persons face, such as minority stress, low social support, and discrimination. A possible role of minority stress is seen in the cluster of anxiety symptoms, where anxious feelings and panic show strong associations with sensitivity to rejection and low self-image.

Notably, we did not find a significant decrease in depressive symptoms in the overall cohort after start of GAHT, in contrast with previous studies (Costa and Colizzi, 2016; Doyle et al., 2023). This discrepancy could have numerous explanations. Firstly, mood may be influenced by the timing of the baseline measurement: in the ENIGI and RESTED cohorts, the participants already knew they were going to start GAHT soon
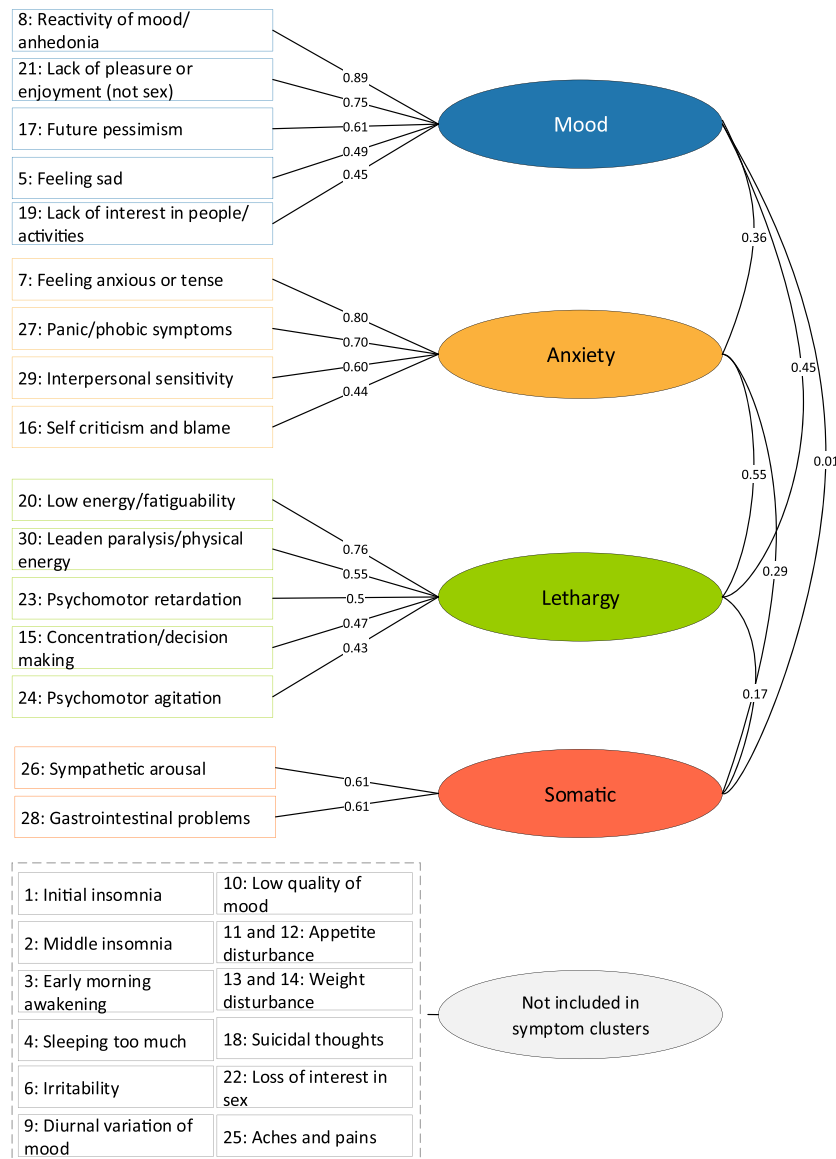
Fig. 3. Path diagram of clusters of items from the IDS-SR at baseline, as found in the EFA analysis. Arrows connecting items (in rectangles) and clusters (in ellipses) represent factor loadings, arrows between the factors (ellipses) represent correlation coefficients between the factors. Only items with loadings >0.4 were included in the symptom clusters. Symptoms with factor loadings below 0.4 were not included in the symptom clusters and are displayed in grey below the path diagram.

at the baseline measurement, and stress or excitement about starting GAHT could have affected their mood. Secondly, the IDS-SR data of this study was not accessible to healthcare providers, whereas study data from previous studies was often obtained from clinical care. This addresses a concern that was previously noted (Baker et al., 2021), which is that participants could provide socially desirable answers when they know that their healthcare providers can access their answers, out of fear of losing access to GAHT.

We find significant differences between the changes in IDS-SR scores between the users of feminizing and masculinizing GAHT, and the opposing directions of the findings are is in line with depression in cisgender men and women. However, it must be noted that the absolute differences between the groups, with the TM group reporting an estimated 10 % decline in depressive symptoms, which would translate into a median decrease of 1.5 points, and the TF group reporting an estimated increase of 16 %, which would translate in a median increase of 1.8 points, resulting in an estimated 3.3 point difference in IDS-SR score changes after 12 months of GAHT. Although we had no predefined minimal clinically important difference, we believe that these changes

might not directly translate into clinically significant effects.

This discrepancy between the TM and TF groups is seen more specifically in the subscales of the clusters. The subscale for mood symptoms increases in the TF group by 24 % after 12 months of GAHT but shows no significant changes in the TM group. The increase in mood symptoms in transgender women is in line with findings in the cisgender female population, where sex hormone interventions in reproductive-age participants have been associated with anhedonia and low mood (Frokjaer, 2020; Schiller et al., 2022). Secondly, the lethargy symptoms show no changes in the TF group, but a temporary decrease in the TM group after 3 months of GAHT. There are no studies on reported energy levels or lethargy symptoms in transgender testosterone users, but this finding is in line with a study in hypogonadal males, where 8 weeks of testosterone use resulted in decreased fatigue and increased vigor (O'Connor et al., 2002).

The most important strengths of this current study are the prospective cohort design and the data-driven approach to studying depressive symptoms. The prospective, within-person design can more accurately give insight into changes in depressive symptoms after GAHT use, and

Table 2
Results show the estimated changes in IDS-SR scores and subscale scores after 3 and 12 months of GAHT in all participants who contributed a baseline and at least one follow-up measurement. Each cell displays the median score and corresponding 25th and 75th percentile, and follow-up time points display the estimated percentages of change relative to baseline, the corresponding 95 % confidence interval and *p*-value.

	Overall cohort			Transmasculine participants			Transfeminine participants		
Time point	Baseline	3 months	12 months	Baseline	3 months	12 months	Baseline	3 months	12 months
n	135	125	85	80	70	54	56	55	31
Total	13 (8 to 24.3)	15 (10 to 20) −0.8 %, (−10.1 %; 9.4 %), p = 0.87	14 (9 to 22) −1.3 %, (−11.7 %; 10.3 %), p = 0.83	15 (9 to 26.5)	15 (9.3 to 19.8) −9.9 %, (−20.7 %; 2.3 %), p = 0.11	14 (8.3 to 24.8) −10.3 %, (−21.9 %; 3.1 %), p = 0.13	11.5 (6.8 to 21)	13 (10 to 19.5) 12.6 %, (−2.8 %; 30.5 %), p = 0.12	13 (9 to 21.5) 15.8 %, (−3.1 %; 38.4 %), p = 0.11
Mood	2 (0 to 3)	2 (0 to 3) −2.3 %, (−12.1 %; 8.6 %), p = 0.66	2 (0 to 4) 3.2 %, (−8.5 %; 16.3 %), p = 0.61	2 (0 to 3)	2 (0 to 3) −4.9 %, (−17.1 %; 9.2 %), p = 0.48	1 (0 to 3.8) −7.1 %, (−20.1 %; 7.9 %), p = 0.34	2 (1 to 3)	2 (1 to 3) 1.1 %, (−13.8 %; 18.6 %), p = 0.89	2 (1.5 to 4.5) 24.3 %, (2.6 %; 50.6 %), p = 0.03
Anxiety	2 (0 to 5)	2 (0 to 4) −5.7 %, (−14.5 %; 4.1 %), p = 0.25	2 (0 to 3) −4.2 %, (−14.3 %; 7.1 %), p = 0.46	2 (0 to 5)	2 (0 to 3.8) −4.2 %, (−16.0 %; 9.1 %), p = 0.45	2 (0 to 3.8) −2.8 %, (−15.6 %; 12.0 %), p = 0.63	2 (1 to 4)	2 (0 to 4) −7.7 %, (−20.7 %; 7.3 %), p = 0.30	1 (0.5 to 3) −5.9 %, (−21.5 %; 12.7 %), p = 0.51
Lethargy	2 (0 to 5)	2 (0 to 4) −7.7 %, (−18.2 %; 4.0 %), P = 0.19	2 (1 to 4) 1.3 %, (−11.6 %; 15.9 %), p = 0.86	2.5 (0.8 to 5)	2 (0 to 4) −16.3 %, (−28.5 %; −2.0 %), p = 0.03	2 (1 to 4.8) −2.3 %, (−17.7 %; 15.9 %), P = 0.79	1.5 (0 to 4)	2 (0 to 4) 4.7 %, (−12.8 %; 25.7 %), P = 0.62	1 (0 to 4) 7.1 %, (−14.1 %; 33.3 %), P = 0.54
Somatic	0 (0 to 1)	0 (0 to 1) 1.3 %, (−7.5 %; 11.1 %), P = 0.77	0 (0 to 1) 3.0 %, (−7.1 %; 14.1 %), P = 0.58	1 (0 to 1)	0 (0 to 1) −4.4 %, (−15.3 %; 7.7 %), P = 0.46	1 (0 to 1) 3.8 %, (−8.8 %; 18.2 %), P = 0.58	0 (0 to 1)	0 (0 to 2) 9.6 %, (−4.6 %; 25.9 %), P = 0.20	0 (0 to 1) 1.0 %, (−14.4 %; 19.2 %), P = 0.91

the EFA analysis provided insight going further than the sum of all depressive symptoms, showing that especially mood and lethargy symptoms were prone to change after GAHT use. The identified subscales of the IDS-SR also enable further study into depression in transgender persons and GAHT use.

However, there are several limitations that should be taken into account in the interpretation of our results. First, the study's one-year follow-up period is relatively short compared to the expected long-term use of GAHT. During the first year of GAHT, people experience physical changes, but also changes in their social environment, such as changes in support from loved ones or confrontation with discrimination and stigmatization (Collet et al., 2023b). It is likely that getting used to both the physical and social changes during this transition may take more than just one year, and longer follow-up is needed.

Second, there may be selection bias in participant inclusion and follow-up, possibly impacting our findings. The exclusion of individuals with diagnosed sleep disorders in the RESTED study could lead to underestimation of insomnia symptoms. Furthermore, participants with mental health issues might be less likely to participate. However, when comparing the psychiatric history of the current study participants, we see that 47 % of our current participants had a lifetime mood disorder, compared to 60 % of participants in Heylens et al. (2014) and 34.5 % in Defreyne et al. (2019), showing no indications of selection bias from psychiatric history. There also is loss to follow up in the study, and GAHT users who experienced more or less depression-related side effects could have been more likely to drop out. Addressing this bias, we compared IDS-SR score severity and baseline IDS-SR scores between participants who were and were not lost to follow-up, as displayed in Supplementary Table 5. These comparisons reveal no significant differences between the groups, indicating no selective loss to follow-up. Nonetheless, the loss of power due to loss to follow-up should be taken into account in the interpretation of the study results, and further replication is necessary.

Third, as shown in the EFA results, not all items from the IDS-SR

could be included in the resulting subscales due to low factor loadings. An EFA analysis is based on associations between questionnaire items, and low factor loadings are generally seen in items that lack strong associations with the other questionnaire items. This can be caused by low variability in the item, lack of specificity in the item or lack of associations with other items. For this study, we opted to exclude items with factor loadings below 0.4, to obtain more valid and reliable subscales, but this also led to the exclusion of numerous items from the subscales.

Fourth, the use of the IDS-SR also has limitations in clinical applicability. It is a self-report questionnaire on depressive symptoms and it can therefore not be used to diagnose depression. Additionally, the IDS-SR measures depressive symptoms and negative mood, not taking into account increases in positive mood or well-being. The TF group might experience increases in both positive and negative emotion intensity (Matthys et al., 2021; Slabbekoorn et al., 2001; Wierckx et al., 2012). If increased emotionality would result in increases in both positive and negative moods, the IDS-SR would only detect increased negative mood. It is possible that neurobiological changes, such as changes in neuroactive steroids and neurotransmitters (Collet et al., 2021; Kiyar et al., 2022) or psychosocial changes (as reviewed by Doyle et al., 2023) contribute to changes in mood, and further research should focus on the intersection of biological and psychosocial changes in GAHT users.

Lastly, the current study did not address possible within-group differences which could be driven by differences in gender identity, hormone formulations or hormone level dynamics. Previous work has shown that transgender persons with an non-binary gender identity report poorer mental health compared to persons with a binary gender identity (i.e. (transgender) man or woman; de Graaf et al., 2021), which indicates that both hormone use and gender identity could be of importance for mental well-being in transgender GAHT users. Furthermore, based on literature in cisgender women, especially work indicating a possible role of "sex hormone withdrawal" it is also possible that differences in hormone forms and resulting differences in hormone
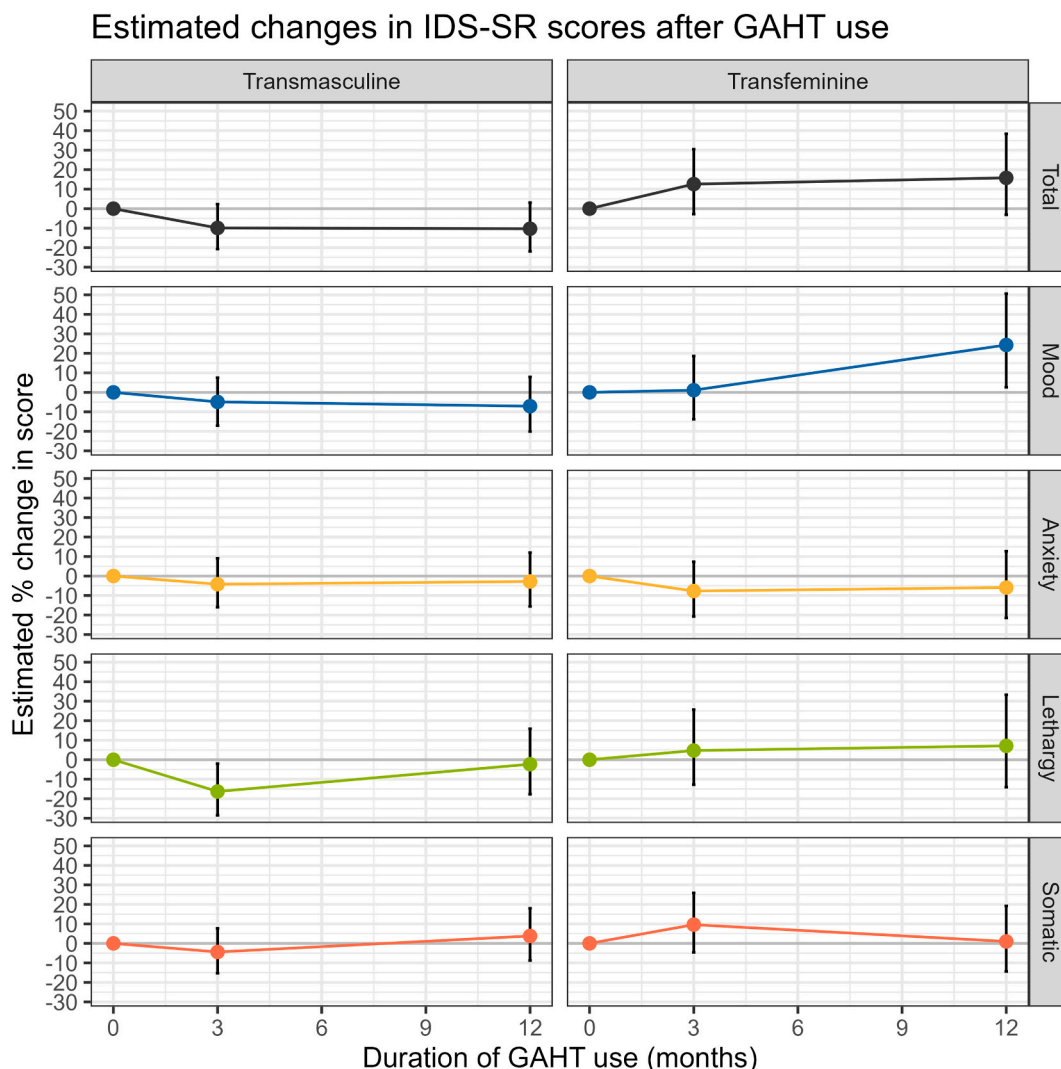
Fig. 4. Estimated change in IDS-SR scores and subscales after 3- and 12 months of GAHT, displayed per group. The y-axis displays estimated % of change, error bars display the 95 % confidence intervals of the estimates. Increases in scores indicate worsening in symptoms, i.e. an increase in total depressive symptom score means the participant reports more depressive symptoms.

levels, dynamics and possible lack of suppression of the menstrual cycle could affect mood (Frokjaer, 2020; Schiller et al., 2022). Although sensitivity analyses (reported in Supplementary Table 2) showed no significant differences between different forms of estrogen and testosterone, future studies are necessary to better address the role of hormone dynamics in mood in transgender GAHT users.

In the interpretation of our results for clinical practice, it is important to consider that the primary aim of GAHT use is to reduce gender dysphoria, and that starting GAHT is a long-awaited major life event for many transgender persons. Studies show that GAHT use results in decreases in gender dysphoria (Foster Skewis et al., 2021; van Leerdam et al., 2021) and that rates of regret are very low (Wiepjes et al., 2018). Therefore, the increase in low mood in the transfeminine group should be interpreted with caution, and replication and further research on underlying causes is necessary.

Our results reveal distinct changes in the depression symptom profiles between masculinizing GAHT users compared to feminizing GAHT users, aligning with prevalence differences found in cisgender populations. These findings support the hypothesis that masculinizing or feminizing hormones could affect depressive symptoms differently. They also raise new questions on possible mechanisms related to depressive symptoms and sex hormone use, which could also be relevant for other populations using exogenous sex hormones. Future research on

GAHT and depression should focus on interactions with psychosocial factors (e.g. stress, discrimination, or support) and biological changes (e. g. genetic and neurobiological factors). This will eventually aid in developing more gender-sensitive mental health care.

CRediT authorship contribution statement

Margot W. L. **Morssinkhof**: Conceptualization, Methodology, Investigation, Formal analysis, Writing – Original Draft, Visualization. **Chantal M. Wiepjes**: Investigation, Data Curation, Project administration, Writing – Review and Editing. **Odile A. van den Heuvel**: Conceptualization, Methodology, Writing – Review and Editing, Supervision. **Baudewijntje P.C. Kreukels**: Writing – Review and Editing. **Karin van der Tuuk**: Investigation. **Guy T'Sjoen**: Writing – review & editing. **Martin den Heijer**: Methodology, Investigation, Data Curation, Writing – Review & Editing, Supervision. **Birit F.P. Broekman**: Conceptualization, Methodology, Investigation, Writing – First Draft and Review & Editing, Supervision.

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involvement in the study design, data collection, analysis or interpretation of the data, writing of the report or decision to submit the article. All other authors have no financial conflicts of interest.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.12.056.

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