Sleep Medicine 107 (2023) 316–326

Contents lists available at ScienceDirect

Sleep Medicine

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

Sex hormones, insomnia, and sleep quality: Subjective sleep in the first year of hormone use in transgender persons

Margot W.L. Morssinkhof [a, b, c, k, *], Chantal M. Wiepjes [c, k], Breanna W. Bosman [a], Jim Kinds [a], Alessandra D. Fisher [d], Yona Greenman [e], Baudewijntje P.C. Kreukels [f, k], Guy T'Sjoen [g], Ysbrand D. van der Werf [h, i], Martin den Heijer [c, k], Birit F.P. Broekman [a, b, j]

[a] Amsterdam UMC, Location Vrije Universiteit Amsterdam, Department of Psychiatry, Boelelaan 1117, Amsterdam, the Netherlands
[b] OLVG Hospital, Department of Psychiatry and Medical Psychology, Amsterdam, the Netherlands
[c] Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Endocrinology, Department of Internal Medicine, Amsterdam, the Netherlands
[d] Andrology, Women's Endocrinology and Gender Incongruence Unit, Florence University Hospital, Florence, Italy
[e] The Institute of Endocrinology, Diabetes, Metabolism and Hypertension, Tel Aviv-Sourasky Medical Center and Tel Aviv University, Tel Aviv, Israel
[f] Department of Medical Psychology, Amsterdam UMC, Vrije Universiteit Amsterdam, the Netherlands
[g] Dept. of Endocrinology and Centre for Sexology and Gender, Ghent University Hospital, Gent, Belgium
[h] Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Anatomy and Neuroscience, Amsterdam, the Netherlands
[i] Amsterdam Neuroscience, Compulsivity Impulsivity and Attention, Amsterdam, the Netherlands
[j] Singapore Institute for Clinical Sciences, Agency for Science, Technology and Research (A*STAR), Singapore
[k] Amsterdam UMC, Vrije Universiteit Amsterdam, Center of Expertise on Gender Dysphoria, Amsterdam, the Netherlands

ARTICLE INFO

Article history:
Received 20 February 2023
Received in revised form
20 April 2023
Accepted 27 April 2023
Available online 20 May 2023

Keywords:
Insomnia
Sleep quality
Endocrinology
Estrogen
Testosterone
Transgender

ABSTRACT

Study objectives: Transgender persons can use gender-affirming hormone therapy (GAHT) to align their physical appearance with their identified gender. Many transgender persons report poor sleep, but the effects of GAHT on sleep are unknown. This study examined the effects of a 12 months of GAHT use on self-reported sleep quality and insomnia severity.
Methods: A sample of 262 transgender men (assigned female at birth, started masculinizing hormone use) and 183 transgender women (assigned male at birth, started feminizing hormone use), completed self-report questionnaires on insomnia (range 0–28), sleep quality (range 0–21) and sleep onset latency, total sleep time and sleep efficiency before start of GAHT and after 3, 6, 9, and 12 months of GAHT.
Results: Reported sleep quality showed no clinically significant changes after GAHT. Insomnia showed significant but small decreases after 3 and 9 months of GAHT in trans men (−1.11; 95%CI: -1.82; −0.40 and −0.97; 95%CI: -1.81; −0.13, respectively) but no changes in trans women. In trans men, reported sleep efficiency decreased by 2.8% (95%CI: -5.5%; −0.2%) after 12 months of GAHT. In trans women, reported sleep onset latency decreased by 9 min (95%CI: -15; −3) after 12 months of GAHT.
Conclusions: These findings show that 12 months of GAHT use did not result in clinically significant changes in insomnia or sleep quality. Reported sleep onset latency and reported sleep efficiency showed small to modest changes after 12 months of GAHT. Further studies should focus on underlying mechanisms by which GAHT could affect sleep quality.

1. Introduction

Many people experience poor sleep quality: they report trouble falling asleep, staying asleep, or waking up early. Globally, between 36% and 57% of people report poor sleep [1–3], although estimates vary widely. If the burden of these symptoms significantly impairs daily life it can be defined as insomnia disorder. Insomnia is the second most common mental disorder in Europe [4], with an estimated 30%–36% of the population reporting at least one insomnia symptom [5]. The burden of insomnia is not distributed equally over the population. In cisgender populations, women of reproductive age are 1.5 times more likely to experience insomnia [6] and they report worse sleep quality than men, as seen in longer

* Corresponding author. Amsterdam UMC, Location VUmc, Department of Psychiatry, De Boelelaan 1117, 1081 HV, Amsterdam, the Netherlands.
E-mail address: m.morssinkhof@amsterdamumc.nl (M.W.L. Morssinkhof).

https://doi.org/10.1016/j.sleep.2023.04.028

sleep onset latencies, more sleep disturbances, and lower sleep efficiency [7,8]. Although studies suggest that gender-specific factors, such as social expectations, care duties and a higher prevalence of mood disorders, contribute to more insomnia and worse sleep quality in women [9–11], epidemiological studies also suggest that biological factors, such as sex hormones, can also affect sleep quality.

There are several indications of associations between sex hormones and sleep quality throughout the lifespan. Firstly, the sex difference in insomnia prevalence starts from puberty onwards, with cisgender girls reporting more insomnia than cisgender boys [12]. In this period the timing of onset of the first menstruation, which is triggered by sex hormone changes, is specifically associated with an increase in insomnia risk [13]. Secondly, symptoms of insomnia also increase during pregnancy [14] and perimenopause [15], which are both life phases in which sex hormones strongly fluctuate. Lastly, in cisgender men, who experience less marked sex hormone fluctuations in their lifetime after puberty, there seems to be a bidirectional relationship between testosterone and sleep. Disturbed sleep seems to result in lower testosterone levels [16] and vice versa, lower testosterone seems to be associated with poorer sleep quality [17] and with shorter sleep duration [18].

Studies on the influence of sex hormone interventions on sleep also show possible sex hormone-induced changes in sleep quality. In cisgender women, an experimental suppression of sex hormone production through administration of gonadotropin-releasing hormone (GnRH) analogs, led to decreased sleep quality [19]. These effects were unrelated to the mood disturbance effects of the GnRH intervention [19]. Studies also suggest that oral contraceptives, which most commonly contain exogenous estrogens and progestogens and suppress sex hormone endogenous fluctuations, can increase reported insomnia symptoms [20,21]. On the other hand, the reinstatement of stable sex hormone levels during perimenopause through hormone replacement therapy (HRT), which is a regimen of both estrogens and progestogens, seems to improve sleep quality [22]. In cisgender men, suppression of testosterone production seems to decrease sleep quality, since it increases sleep onset latency and decreases deep sleep [23]. In hypogonadal cisgender men with poor sleep, results still seem inconclusive: testosterone replacement therapy seems to improve sleep quality [24] and shorten sleep duration [25], but studies on testosterone use and sleep are still scarce. One limitation of many studies on sex hormones and sleep is that they have mainly included participants who are hypogonadal or going through perimenopause, meaning their endogenous hormone levels are already low or changing and it is difficult to generalize these findings to the wider population [26]. Therefore, knowledge of the effects of sex hormones on sleep so far has been limited.

The effects of sex hormone use can be studied in transgender persons who use gender-affirming hormone therapy (GAHT). In contrast to cisgender persons, transgender persons experience an incongruence between their sex assigned at birth and their gender identity. Many transgender persons seek treatment with GAHT in order to align their physical features with their identified gender. Generally, the use of GAHT is associated with improved body image and quality of life [27]. Trans men, who were assigned female at birth, can be prescribed masculinizing hormones, most commonly a form of testosterone. Trans women, who were assigned male at birth, can be prescribed feminizing hormones, often consisting of a form of estrogen combined with anti-androgens. Sleep problems are common in the transgender population: up to 80% of transgender persons report that they experience poor sleep [28]. However, up till today the effect of GAHT on insomnia and sleep quality has not yet been studied.

Therefore, this study will prospectively assess self-reported insomnia symptoms and sleep quality during GAHT use in transgender persons. This study firstly aims to study the trajectory of insomnia symptoms and sleep quality during the first 12 months of GAHT. Secondly, it aims to assess changes in sleep onset latency, total sleep duration, and sleep efficiency after 12 months of GAHT. Thirdly, as hot flashes are a common side effect of estrogens and anti-androgens [29], we explore whether hot flashes play a moderating role in the relation between GAHT and insomnia.

Based on differences in insomnia and sleep quality in the cisgender population, we hypothesize that after 12 months of GAHT, trans men will report fewer insomnia symptoms and better sleep quality, and trans women will report more insomnia symptoms and worse sleep quality. We also hypothesize that participants who experience hot flashes will report more insomnia symptoms.

2. Methods

2.1. Study participants

Transgender persons who participated in the endocrinological part of the European Network for the Investigation of Gender Incongruence (ENIGI) study were included. ENIGI is an ongoing prospective cohort study that aims to investigate the clinical effects and side effects of GAHT in Oslo (Oslo University Hospital), Ghent (University Hospital Ghent), Tel Aviv (Souraski Hospital), Florence (University Hospital Florence), and Amsterdam (Amsterdam University Medical Center) [30]. For the current analysis, data was collected from the centers in Ghent, Tel Aviv, Florence, and Amsterdam. Participants were included at the start of GAHT if they were aged 17 or older (Ghent) or aged 18 years or older (Tel Aviv, Florence, and Amsterdam), native in their national language (Flemish, Hebrew, Italian, or Dutch) and had a confirmed diagnosis of gender dysphoria according to the DSM-4 or DSM-5, depending on when they were diagnosed. Ethics approval was granted by the local medical ethical committees in Ghent, Tel Aviv, and Florence. In Amsterdam, the medical ethical committee declared that the Medical Research Involving Human Subjects Act (WMO) did not apply to this the data collection of the ENIGI study. All participants received written and oral information, after which they signed informed consent according to the institutions' guidelines. Participants received GAHT in accordance with Standards of Care of the World Professional Association for Transgender Health (WPATH), edition 7 [31]. The sleep measures (the Insomnia Severity Index (ISI) and Pittsburgh Sleep Quality Index (PSQI)) were collected from July 2017 until October 2021. Prior to the start of analyses, the analysis plan of this study was preregistered at the Open Science Framework (OSF) under DOI 10.17605/OSF.IO/JSCPW [32]. For the purposes of this study we grouped all users of masculinizing GAHT under "trans men" and all users of feminizing GATH under "trans women". We acknowledge and recognize that these particular labels may not represent the personal identities of all participants involved.

2.2. Inclusion criteria and data cleaning

Fig. 1 displays the participant flowchart. Of all ENIGI participants, 467 participants filled out the sleep questionnaires. Participants were excluded if they had undergone gonadal surgery (n = 2), had already used GAHT at the baseline measurement (n = 5), if their baseline measurement was conducted more than a week after the start of GAHT (n = 3), or if they did not start using the prescribed GAHT after the first GAHT appointment (n = 5).

A small proportion of participating trans women did not use estrogens (n = 4) or did not use anti-androgens (n = 3), these participants were also excluded from the current analysis. This resulted in a final sample size of 445 participants, of whom 262

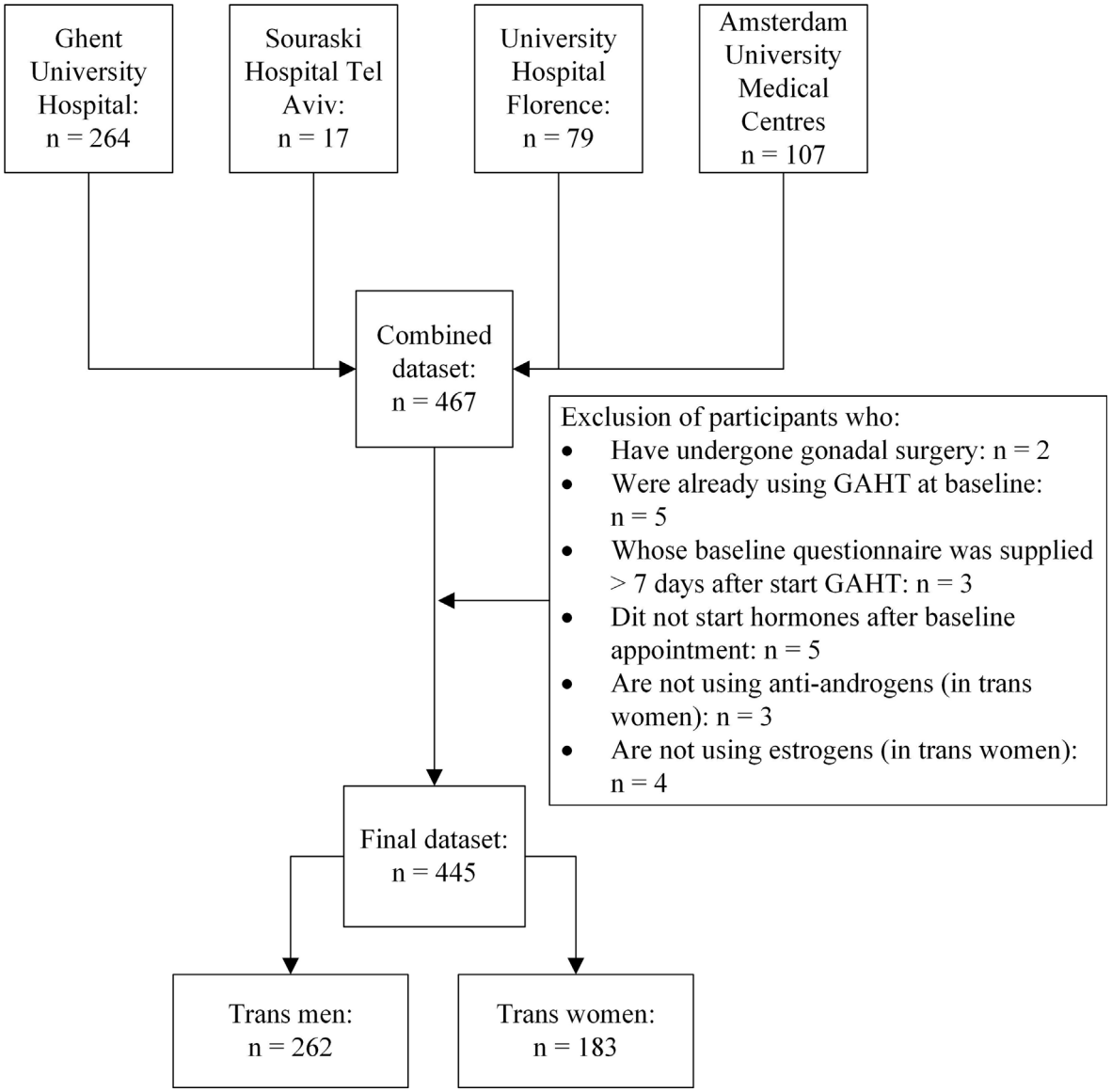

Fig. 1. The number of unique participants (n) per center and group, before and after applying exclusion criteria. Total n reflects the number of unique participants contributing to any measurement.

trans men and 183 trans women. Due to the ongoing character of the study and the fact that not all centers participated in all measurement time points, the consecutive sample sizes at follow-up measurements differ from the baseline sample size; the respective sample sizes at follow-up are also displayed in the results.

2.3. Gender-affirming hormone therapy

Masculinizing hormones used by trans men consisted of testosterone gel (daily dose of 40.5 mg), intramuscular testosterone esters (250 mg every 3 weeks), or intramuscular testosterone undecanoate (1000 mg every 12 weeks). For participants who reported persisting menstruation or intermittent menstrual blood loss, continued use of hormonal contraceptives (i.e. injectable medroxyprogesterone, subcutaneous implant containing etonogestrel, intra-uterine device containing levonorgestrel, or combined oral contraceptives) or use of progestogens as menstruation suppressants (lynestrenol, 5 mg per day) was recommended. Use of menstruation suppressants and hormonal contraceptives in the trans men was grouped under the term cycle-regulating medication. Feminizing hormones used by transgender women consisted of the anti-androgen cyproterone acetate (CPA; daily dose of 10–50 mg), or GnRH analogs, i.e. either the short-acting form (triptorelin 3.75 mg per 4 weeks) or the long-acting form (triptorelin 11.25 mg per 12 weeks), combined with estrogens, i.e. either orally administered estradiol valerate (2 mg twice daily), estradiol gel (0.06% 1.5 mg daily) or estradiol patches (100 mcg per 24 h twice a week). All included trans women used both estrogens and anti-androgens.

2.4. Questionnaires

Self-reported symptoms of insomnia and sleep quality were assessed using the ISI [33] and PSQI [34]. The ISI scores were assessed at baseline and after 3-, 6-, 9- and 12 months of GAHT, and the PSQI was assessed at baseline and after 12 months of GAHT. The ISI is a seven-item questionnaire that inquires about reported symptoms of insomnia and the daily burden of insomnia in the

previous two weeks. Each item ranges from 0 to 4, and items are added together to form a sum score (range 0–28), where a higher score means more severe insomnia symptoms. To estimate the presence of insomnia, the ISI scores can be grouped using the standardized cut-offs: a score of 7 or lower indicates the participant experiences no insomnia, a score between 8 and 14 mild or subclinical insomnia, a score between 15 and 21 moderate or clinical insomnia, and a score over 22 severe clinical insomnia [33]. Although the ISI has not been validated in a cohort of transgender persons, it has excellent internal validity (Cronbach's alpha = 0.90 [35]) it is widely used in sleep research to indicate the severity of insomnia symptoms [36]. The seven items directly correspond to the symptoms of insomnia as defined by the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders [37].

The PSQI is a questionnaire that consists of 19 items, and each item can be scored on a range from 0 to 3. It inquires about subjectively reported sleep duration, sleep quality, sleep disturbances, and daytime disturbances due to sleep problems over the past month. It is scored into seven subscores, which are subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. Each subscore is calculated from specific items of the questionnaire, and the total sum of the seven components forms the total score of the PSQI (scale 0–21), which can be used as a proxy of reported sleep quality. The PSQI is used as a broader measure of sleep quality, since it also inquiries about sleep- and wakeduration, and has the ability to discriminate “good” from “poor” sleepers using a cutoff score of 5: a score of 5 or lower indicates good quality sleep, while a score of higher than 5 indicates poor quality sleep [34]. Additionally, the PSQI also asks about the time spent trying to fall asleep (i.e. the sleep onset latency or SOL), the total number of hours of sleep per night (total sleep time or TST), and the total time spent in bed, which can be used to calculate sleep efficiency (or SE; i.e. the % of time in bed that is actually spent sleeping).

2.5. Lifestyle and medication

Drug and alcohol use were either self-reported in questionnaires (Amsterdam) or asked by healthcare professionals and recorded in medical files (Ghent, Tel Aviv, Florence). Body Mass Index (BMI) was calculated using participants’ weight, which was measured in light indoor clothing without shoes at clinical visits using a digital floor scale, and their height, also recorded during clinical visits. Medication use was recorded in medical files. Due to the possible effects of psychotropic medications on sleep, for this study the psychotropic medication use was grouped based on WHO-defined ATC codes into the use of antidepressants (ATC code N06A), stimulants (ATC code N06B), antipsychotics (ATC code N05A), sedative medication use (ATC codes N05B and N02A), or mood stabilizers (ATC code N05AN).

2.6. Moderation variables

In order to test the possible moderation effect of hot flashes on insomnia, reported hot flashes were recorded using item 1 from the menopause rating scale [38] (MRS). This item was dichotomized into either no hot flashes (e.g. “None” or “Mild”) or hot flashes (e.g. “Moderate”, “Severe”, “Very Severe”), and included in our models as an interaction term with the duration of GAHT. In our preregistration, we also proposed to analyze interaction effects of cycle regulation use and having undergone mastectomy surgery. However, due to underpowered samples in cycle regulation analyses and the high likelihood of selection bias in mastectomy surgeries, the results of both analyses are only reported in the supplementary materials.

2.7. Statistical analyses

Statistical analyses were conducted using Rstudio (version 4.1.2), combined with the lme4 package [39] and the lmerTest package [40]. We used descriptive statistics to describe the prevalence of insomnia and poor sleep at the start of GAHT in both trans men and trans women, describing the number of participants qualifying for scores indicating (subclinical) insomnia and poor sleep quality using total numbers and percentages. To analyze the changes in ISI and PSQI scores, we used linear mixed models with a random intercept per participant and a random intercept per center, to account for the repeated measures per participant and nested participants within the participating centers. Analyses were conducted separately for trans men and trans women. Missing values in the PSQI and ISI variables were deleted listwise per model analysis, and results were interpreted using the fixed effect estimates and 95% confidence intervals.

In the first unadjusted model, time of measurement was used as the only fixed predictor in the unadjusted model. Secondly, the variables age, BMI, alcohol use (categorized into 0 drinks per week, 1 to 7 drinks per week, or more than 7 drinks per week), and psychotropic medication use (dichotomized in use and no use) at each measurement point were incorporated as fixed factors in the models to see if they improved model fits. This resulted in a final adjusted model, which included alcohol use and psychotropic medication use as confounder variables, also displayed below as the adjusted model (see Table 1). For post-hoc analyses, we tested the aforementioned moderators as interaction terms together with the time of measurement in separate models to see whether the interaction term affected the association between sleep outcomes and the duration of GAHT use. This resulted in the models as reported in Table 1, analyzed in trans men and women separately.

3. Results

3.1. Demographic characteristics

As displayed in Table 2, the median age in trans men was 23.2 years (IQR = 20.4; 29.5). The majority of trans men did not use psychotropic medication (n = 230, 87.8%) or drugs (n = 154, 85.1%). At the start of GAHT use, long-acting intramuscular testosterone undecanoate was the most common form of prescribed testosterone (n = 176, 67.2%) in trans men. The median age of trans women was 27.5 years old (IQR = 22.8; 36.6), and most did not use psychotropic medication (n = 156, 85.4%) or drugs (n = 154, 84.3%). At the start of GAHT in the trans women, oral estradiol valerate was the most common form of prescribed estrogens (n = 132, 72.1%) and CPA was the most common form of prescribed anti-androgens (n = 151, 82.5%). The resulting serum hormone values are also displayed in the supplementary materials.

3.2. Insomnia

The ISI scores indicate that 55.9% of trans men report no insomnia at baseline, 35.5% show mild insomnia, 8.0% show moderate insomnia, and 0.5% show severe insomnia. ISI scores in trans women at baseline indicate that 60.0% of trans women report no insomnia, 31.4% show mild insomnia, 7.9% show moderate insomnia, and 0.7% show severe insomnia. After 12 months of GAHT, the insomnia scores in the trans men show that 55.1% report no insomnia, 36.4% report mild insomnia, 7.5% report moderate insomnia and no participant reports severe insomnia. After 12 months of GAHT in the trans women, ISI scores show that 63.8% of participants report no insomnia, 30% reports mild insomnia, 6.3% reports moderate insomnia and no participant reports severe

Table 1
Linear mixed models used for the statistical analysis.

Model	Outcome
Unadjusted	Sleep outcome[a.] ~ measurement time point + (1|participant ID) + (1|center)
Adjusted	Sleep outcome[a.] ~ measurement time point + alcohol use + psychotropic medication use + (1| participant ID) + (1|center)
Moderator	ISI score[b.] ~ measurement time point * moderator + (1| participant ID) + (1|center)

[c]. As displayed in results: reported hot flashes (yes/no), as displayed in supplementary materials: having undergone a mastectomy, using cycle regulation medication.
[a] The following outcomes were tested: ISI score, PSQI score, TST, SOL and SE.
[b] The moderator models were only tested on the ISI scores, since the PSQI scores were only available at baseline and 12 months after GAHT.

Table 2
Baseline demographic characteristics of the participants.

	Trans men (n = 262)	Trans women (n = 183)
Age (years; median (IQR))	23.2 (20.4; 29.5)	27.5 (22.8; 36.6)
BMI (kg/m^2; median (IQR))	24.1 (20.8; 28.4)	22.4 (19.4; 26.8)
Alcohol (n, %)		
Never drinker	100 (38.2%)	69 (37.7%)
1 to 7 drinks per week	112 (42.7%)	75 (41.0%)
7+ drinks per week	10 (3.8%)	8 (4.4%)
Missing	40 (15.3%)	31 (16.9%)
Drug use (n, %)		
No drug use	223 (85.1%)	154 (84.1%)
Cannabis use	26 (9.9%)	15 (8.2%)
Hard drug use	0 (0%)	3 (1.6%)
Missing	13 (5.0%)	11 (6.0%)
***Smoking* (n, %)**		
Never	118 (45.0%)	87 (47.5%)
Previous	48 (18.3%)	34 (18.6%)
Current	63 (24.0%)	36 (19.7%)
Missing	32 (12.2%)	26 (14.2%)
Psychotropic medication use [a.] (n, %)		
Antidepressants	27 (10.3%)	17 (9.3%)
Sedative medication	6 (2.3%)	7 (3.8%)
Stimulants	5 (1.9%)	6 (3.3%)
Antipsychotics	5 (1.9%)	2 (1.1%)
Mood stabilizers	0 (0%)	0 (0%)
Testosterone form prescribed at start GAHT (n, %) [b]		
Testosterone gel	69 (26.3%)	–
Testosterone esters	17 (6.5%)	–
Testosterone undecanoate	176 (67.2%)	–
Cycle regulation use at start GAHT (n, %)		
Yes	28 (10.7%)	–
Estrogen form prescribed at start GAHT (n, %) [b]		
Estradiol valerate tablets	–	132 (72.1%)
Estradiol gel	–	18 (9.8%)
Estradiol patches	–	33 (18.0%)
Antiandrogen form prescribed at start GAHT (n, %) [b]		
Cyproterone acetate	–	151 (82.5%)
GnRH analogs (short-acting)	–	29 (15.8%)
GnRH analogs (long-acting)	–	0 (0%)
Spironolactone		3 (1.6%)

IQR = InterQuartile Range.
[a] A single participant could use more than one form of medication at the same time and can therefore be counted multiple times.
[b] Participants could switch the administration form and dosage of GAHT during the study period.

insomnia.

Linear mixed models show that in the trans men, reported ISI scores decrease after 3 and 9 months of GAHT compared to baseline in both the unadjusted model (by −0.96 (95%CI -1.64; −0.29) and −0.91 (95%CI -1.82; −0.40) points, respectively) as well as in the adjusted model (by −1.11 (95%CI -1.82; −0.40) and −0.97 (95% CI -1.81; −0.13) points, respectively) but they show no significant changes after 12 months of GAHT compared to baseline. The trans women report a decrease in ISI scores at 3 months after GAHT of 0.87 (95%CI -1.70; −0.04) points in the unadjusted model, although this is no longer significant in the adjusted model (−0.54, 95%CI -1.43; 0.35). Neither model shows indications of significant changes in reported ISI scores after 6-, 9- or 12 months. Table 3 displays the ISI scores at start of GAHT and after 3, 6, 9, and 12 months of GAHT, and Fig. 2 displays the course of ISI scores over the 12 months of GAHT in both groups.

3.3. Sleep quality

PSQI scores indicate that at baseline, 57% of trans men and 48.7% of trans women report poor sleep quality (PSQI >5) at the start of GAHT. After 12 months of GAHT, 63.3% of the trans men report poor sleep, and the PSQI score in this group is slightly increased in the adjusted model by 0.78 points (95%CI 0.06; 1.50). 48.8% of trans women report poor sleep after 12 months of GAHT, and neither the unadjusted or adjusted models show significant changes in PSQI scores. The PSQI score outcomes are also displayed in Table 3.

3.4. Sleep- and wake durations

In the trans men, the reported total sleep time (TST) and sleep onset latency (SOL) do not show changes in either the adjusted or unadjusted models after 12 months of GAHT. However, trans men's reported sleep efficiency (SE) is estimated to decrease by 2.8% (95% CI: -5.5; −0.2) in the unadjusted model and by 2.7% (95% CI: -5.7; 0.2) in the adjusted model. In the trans women, the reported TST and SE do not show significant changes after 12 months of GAHT, but their reported SOL is an estimated 9 min shorter (95% CI: -15; −3) in the unadjusted model and 10 min shorter (95% CI: -17; −3) in the adjusted model. Fig. 3 also displays the estimated values and 95% confidence intervals of the TST, SOL, and SE per measurement time point and group.

3.5. Post-hoc analyses: moderating factors for insomnia symptoms

Moderation analyses testing the role of hot flashes in trans men show that reported hot flashes do not significantly affect ISI scores at baseline or at follow-up measurements. In the trans women, moderation analyses show significant interactions between hot flashes and ISI scores. Trans women who reported hot flashes report significantly higher ISI scores at the 6- and 9-month follow-up visits compared to trans women who did not report hot flashes (3.07 (95%CI 0.84; 5.29); 3.34 (95%CI 0.96; 5.71), respectively). At the 12-month follow-up, when 27 trans women still experienced hot flashes and 52 participants did not, there was no significant interaction between hot flashes and ISI scores anymore. The mean scores and 95% confidence intervals of trans women with and without hot flashes are also displayed in Fig. 4, and full results of the moderation analyses are reported in the supplementary materials.

4. Discussion

This is the first study to prospectively examine changes in self-reported insomnia and sleep quality during GAHT use in transgender people. Our findings show that before starting GAHT, transgender persons report more poor sleep than insomnia.

Table 3
Total results from the PSQI and ISI per group.

	Trans men			
	Timepoint, months after start GAHT (n)	*Raw scores or durations (median, IQR)*	Unadjusted model *Estimated change from baseline (95% CI: L; H)*	Adjusted model *Estimated change from baseline (95% CI: L; H)*
ISI score *(range 0-28)*	0 (211)	7 (3–11)	Reference	Reference
	3 (172)	6 (3–10)	−0.96 (−1.64; −0.29) **	−1.11 (−1.82; −0.40) **
	6 (120)	7 (3–11)	−0.41 (−1.18; 0.36)	−0.39 (−1.18; 0.39)
	9 (93)	7 (3–10)	−0.91 (−1.73; −0.08) *	−0.97 (−1.81; −0.13) *
	12 (107)	7 (3–11)	−0.04 (−0.82; 0.73)	0.21 (−0.64; 1.06)
PSQI score *(range 0-21)*	0 (200)	6 (4–8)	Reference	Reference
	12 (90)	7 (4–10)	0.49 (−0.17; 1.17)	0.78 (0.06; 1.50) *
TST (hours)	0 (200)	7 (6.5–8)	Reference	Reference
	12 (90)	7 (6–8)	−0.14 (−0.44; 0.16)	−0.22 (6.88; 7.44)
SOL (minutes)	0 (200)	30 (15–45)	Reference	Reference
	12 (90)	30 (15–45)	0.41 (−5.40; 6.20)	−0.09 (−5.41; 6.20)
SE (%)	0 (200)	87.5% (77.8%–94.7%)	Reference	Reference
	12 (90)	84.8% (71.0%–93.6%)	−2.82 (−5.46; −0.23)*	−2.75 (−5.72; 0.19)
	Trans women			
	Timepoint, months after start GAHT (n)	*Raw scores or durations (median, IQR)*	**Unadjusted model** *B (95% CI: L, H)*	**Adjusted model** *B (95% CI: L; H)*
ISI score *(range 0-28)*	0 (140)	6 (3–10)	Reference	Reference
	3 (129)	5 (2–9)	−0.87 (−1.70; −0.04) *	−0.54 (−1.43; 0.35)
	6 (84)	5.5 (2–10)	−0.73 (−1.70; 0.23)	−0.36 (−1.36; 0.64)
	9 (67)	5 (3–9)	−0.10 (−1.12; 0.93)	0.24 (−0.82; 1.30)
	12 (80)	5 (2–9)	−0.61 (−1.60; 0.37)	−0.31 (−1.37; 0.75)
PSQI score *(range 0-21)*	0 (117)	5 (4–8)	Reference	Reference
	12 (62)	5 (3–7)	−0.78 (−1.65; 0.09)	−0.61 (−1.66; 0.34)
TST (hours)	0 (117)	7 (6–8)	Reference	Reference
	12 (62)	7 (6.5–8)	0.28 (−0.13; 0.69)	0.15 (−0.32; 0.62)
SOL (minutes)	0 (117)	25 (11.5–45)	Reference	Reference
	12 (62)	20 (10–30)	−8.91 (−14.94; −3.07) **	−9.61 (−16.56; −2.69) **
SE (%)	0 (117)	88.9% (77.5%–100%)	Reference	Reference
	12 (62)	86.7% (75.0%–91.5%)	−0.01 (−5.17; 2.80)	−0.02 (−5.86; 2.92)

Total ISI score, total PSQI score, as well as reported Total sleep time (TST), Sleep Efficiency (SE%), Sleep onset latency (SOL) obtained from the PSQI in trans men and women, reported per measurement time point. Both mean and IQRs as well as linear mixed model results (from unadjusted and adjusted models) are displayed. * =p <0.05, ** = p < 0.025; IQR = InterQuartile Range; 95% CI = 95% Confidence Interval.

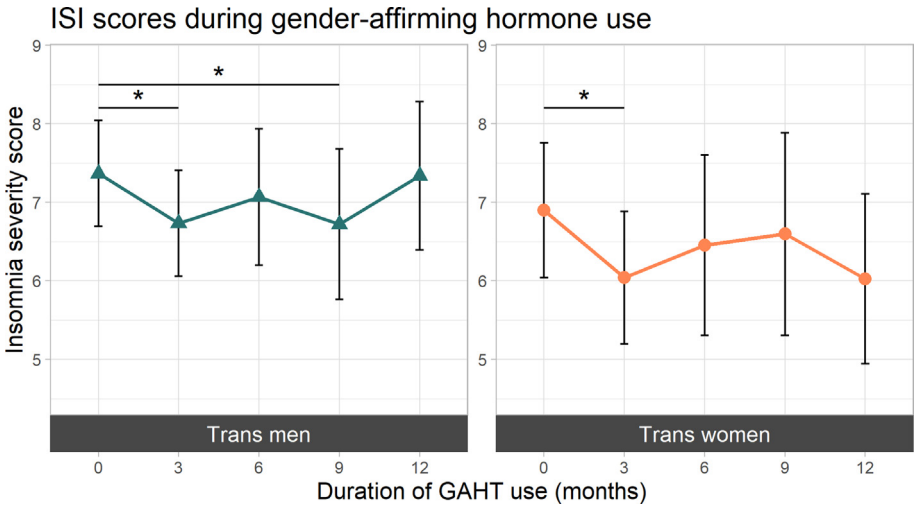

Fig. 2. Estimated mean Insomnia Severity Index (ISI) scores and 95% confidence intervals per participant group and measurement timepoint. Asterisks indicate significant changes (p < 0.05) within the group after 12 months of GAHT. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Overall, the findings show no significant changes in sleep quality and insomnia after 12 months of GAHT. There is a temporary small improvement in symptoms of insomnia after starting GAHT in both trans men and trans women, but the results show no difference in insomnia symptoms and sleep quality after 12 months. Although the subjectively reported total sleep time does not show significant changes after 12 months of GAHT in both groups, trans men report falling asleep 9 min earlier and trans women report an estimated 2.8% decrease in sleep efficiency after 12 months of GAHT. Since a SOL lower than 30 min is seen as healthy [41], the 9-min decrease in trans women could be considered clinically significant. The decrease in SE in the trans men is small compared to the wide range of SE that is considered healthy: An SE higher than 85% is regarded as healthy sleep in adults, and higher than 75% is healthy sleep in

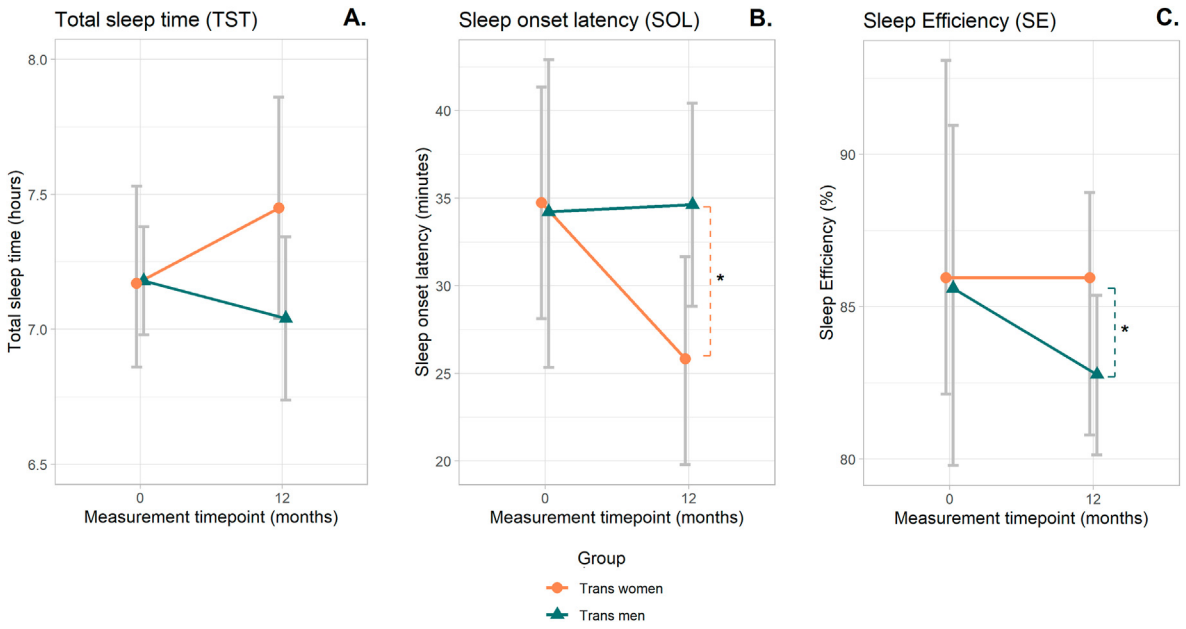

Fig. 3. Pittsburgh Sleep Quality Index (PSQI) outcomes per hormone user group and measurement timepoint, each panel displays the estimated group means and 95% confidence intervals from the unadjusted models. Panel A displays reported total sleep time (TST), panel B displays reported sleep onset latency (SOL) and panel C displays reported sleep efficiency (SE). Dotted lines and asterisks indicate significant changes ($p < 0.05$) within the group after 12 months of Gender-Affirming Hormone Therapy (GAHT); the SOL significantly decreases in the trans women and the SE significantly decreases in the trans men. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

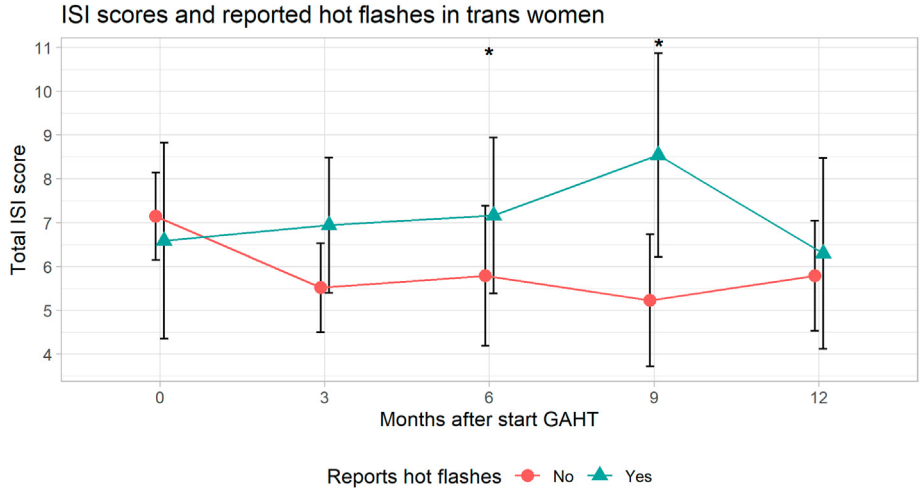

Fig. 4. Mean Insomnia Severity Index (ISI) scores and corresponding 95% confidence intervals of trans women who either did or did not report hot flashes during Gender-Affirming Hormone Therapy (GAHT). Asterisks indicate significant differences ($p < 0.05$) in ISI scores between participants who report hot flashes and participants who do not. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

young adults [41]. A decrease of 2.8% in SE, as seen in trans men, can therefore not be deemed a clinically significant change in SE. Trans women who report hot flashes also report more insomnia symptoms than trans women without hot flashes after 6- and 9 months of GAHT, showing clinically significant but temporary associations between hot flashes and insomnia.

In trans women we expected an increase in reported insomnia symptoms and worse sleep quality after feminizing GAHT, in line with insomnia prevalence in cisgender women. Although we found no overall changes in sleep quality or insomnia in trans women, this group did show a shorter SOL after 12 months. The decrease in SOL may be related to the use of CPA as anti-androgen, since 85% of participating trans women used this at the start of GAHT. CPA is a progestogen with strong anti-androgenic properties, but it can also potently affect both progesterone receptors and glucocorticoid receptors [42]. Previous studies found that administration of progesterone in cisgender men resulted in feelings of fatigue [43], indicating a possible sedative effect of progestogens in a group who naturally have very low progesterone. However, these findings could not be confirmed with objective sleep measures by using sleep electroencephalogram (EEG) measurements in another study [44]. Future research comparing CPA use with, for example, the use of GnRH analogs in a large sample could provide more clarity on the effects of various anti-androgens and SOL duration.

Our findings also showed that trans women who experienced hot flashes reported more severe insomnia symptoms than trans

women who did not experience hot flashes after 6 and 9 months of GAHT use. This is in concordance with studies in cisgender women going through the menopausal transition, which also show that women who experience hot flashes are more likely to report insomnia [45,46]. Hot flashes seem to be associated with low estrogen levels [47], and supplementing estrogen offers symptom relief in postmenopausal women [48]. A similar pattern is also found in persons with prostate cancer who undergo androgen deprivation therapy, for whom hot flashes are a common complaint [49]. In this group, the use of CPA or estrogen supplementation was suggested to reduce the frequency of hot flashes [50,51]. Clinicians working with trans women who report hot flashes could consider monitoring the levels of estrogen to ensure that the estradiol levels are not undersupplied, and they could consider switching the form of anti-androgens to see whether that offers symptom relief from the hot flashes to improve sleep quality.

Although this study in transgender persons on GAHT offers the opportunity to study prospectively the influences of sex hormones on sleep, there are also several limitations. Firstly, many transgender persons describe starting the use of GAHT as a big life event. GAHT comes with physical and mental changes and, for many, it reduces experienced gender dysphoria or depression [52] and improves quality of life [53]. Alleviation of gender dysphoria and depression after GAHT could also affect changes in sleep. Previous research found that transgender people assigned female at birth reported that they experienced sleep disturbances due to the presence of their breasts, which increased gender dysphoria at night [54]. We conducted a post-hoc interaction analysis to see whether trans men who had undergone mastectomy surgery reported more or less insomnia symptoms than trans men who had not and found no differences between the two groups (full results are reported in the supplementary materials). However, it is possible that trans men who experienced more dysphoria because of their chest were more likely to undergo a mastectomy surgery earlier in their transition, so this analysis could likely be biased and was therefore not included in the main results. Secondly, the prevalence of mood disorders in transgender persons who seek gender-affirming care is known to be relatively high: 38% of transgender persons suffer from depressive and anxiety disorders at the time they seek gender-affirming care and almost 70% report a current or lifetime diagnosis of affective disorders [55]. This high prevalence has also been linked to transgender people experiencing gender minority stress [56], which encapsulates the idea that there are specific stressors (such as discrimination and social rejection) and protective factors (such as community support) in transgender people, which can affect their mental health [57]. Since depressive- and anxiety disorders, as well as stress, are strongly associated with insomnia and poor sleep, our participants' mental health could also have affected their sleep. Altogether, in interpreting our study results one should keep in mind that starting GAHT for many transgender people comes with psychological, physical, and social effects (Van Leerdam et al., 2022; Cocchetti et al., 2021) and that many transgender persons suffer from depressive- or anxiety disorders which also affect sleep. Changes after GAHT are most likely multifactorial, such that any changes in sleep could be due to biological as well as social or psychological factors.

Another possible limitation is that we only used self-reported symptoms of insomnia and sleep quality. We did not use objectively measured sleep data (e.g. actigraphy or sleep EEG). Although one could argue that subjective sleep reports are more meaningful than objective measures, since the diagnosis of insomnia is solely based on subjective symptoms, but the subjectively reported sleep- and wake durations, such as the SOL, TST, and SE are most likely less reliable and can be affected by recall bias. Reported sleep durations and durations of wakefulness during the night have been known to often be under- or overestimated when compared to objective sleep durations [58,59]. In cisgender research participants, many studies show that cisgender women show better sleep using objective measurement methods (e.g. longer sleep duration and more deep sleep) compared to cisgender men [60], whereas cisgender women are also more likely to experience insomnia [8]. One small study using sleep EEG measurements in seven trans women found prolonged duration of light sleep after feminizing GAHT use [61]. Further studies using sleep EEG measurements could more accurately study changes in sleep duration, and they could also provide novel insights into possible changes in sleep architecture after GAHT.

At baseline, participating trans men and women show relatively good self-reported sleep: they report a median sleep duration of 7 h, a SOL of 20–30 min, a sleep efficiency above 85% and most participants do not meet the cutoff value for clinically significant symptoms of insomnia. This is remarkable, since transgender people seeking gender-affirming care tend to show high rates of mental health problems [55] and insomnia is an important *trans*-diagnostic symptom of many psychiatric disorders [62]. This might also point to a selection bias in our sample. It is possible that the current study has a selection of relatively healthy participants, especially since our sample also shows low rates of psychotropic medication use. Therefore, these baseline results should be interpreted with caution since it is not clear whether the baseline study sample can be generalized to all transgender persons seeking gender-affirming healthcare.

Our results do not support the hypothesis that the gender disparity in insomnia and poor sleep as seen in cisgender populations can be explained by sex hormones. However, in this context, it is important to note that there is a difference between endogenous and exogenous hormones. There are two important factors in this context: firstly, whether circulating hormones are within the physiological eugonadal range, and secondly, whether wide fluctuations in hormone levels occur.

Most previous studies on sleep and hormones that have been conducted in hypogonadal or perimenopausal persons indicate that strongly fluctuating or clinically low sex hormone levels are associated with insomnia [19,63]. Reinstatement or suppletion of sex hormones in these groups seems to reduce insomnia symptoms [22,24]. This supports the hypothesis that insomnia during hormone changes is mainly caused by hormone levels outside of the physiological healthy range. In our cohort, the protocol of GAHT ensures that GAHT users are not exposed to hormone levels outside of the healthy physiological range: the endogenous sex hormone levels in hormone users are either supplemented (in the case of trans men, by additional testosterone) or replaced by other exogenous sex hormones (in case of trans women, by replacing testosterone by estrogens). The full serum testosterone and estradiol levels are also reported in the supplementary materials. The fact that our participants do not show clinically significant increases in insomnia after GAHT therefore supports the hypothesis that hormone-related insomnia symptoms are mainly associated with hypogonadal hormone levels. Furthermore, this indicates that reinstatement of hormone levels also prevents insomnia, even when giving back estrogen instead of testosterone as is done in trans women. Altogether, the fact that the participating GAHT users are not exposed to induced hypogonadism could explain why neither groups experience increases in insomnia severity.

A second explanation for our findings might also be based on the differences in the dynamics of cisgender persons' hormonal levels as compared to the hormone dynamics of GAHT users. In cisgender women, levels of estrogen and progesterone fluctuate throughout their menstrual cycle, which has been found to affect subjective

sleep quality during certain menstrual phases [59]. In comparison, in trans women the level of estrogen supplementation and androgen suppression is largely constant, although this can still differ based on the administration method of estrogen (e.g. patches or oral administration). This means that trans women likely experience fewer fluctuations in sex hormone levels compared with cisgender women of reproductive age. In cisgender men, testosterone fluctuates daily, whereas in trans men, testosterone levels depend on the administration method of the androgen that is used; the use of daily testosterone gel induces a relatively stable daily testosterone level, but the use of testosterone injections induces 3-week cycle (in the case of testosterone esters) or 12-week cycle (in the case of testosterone undecanoate) of low and high testosterone levels. This means that in testosterone injection users, the level of testosterone fluctuates on a different timescale and in a different manner compared with cisgender men. Based on previous findings that indicate that strong fluctuations in sex hormones are associated with increased insomnia, one could also hypothesize that the amplitude of hormone fluctuations over time irrespective of the type of hormone may be an important determinant of sleep quality. This possible association between hormone fluctuations, irrespective of hormone type, and sleep, might also explain why this study found temporary effects of GAHT on insomnia, but no lasting effects after 12 months of GAHT. It is common for transgender hormone users to change the dosages and forms of GAHT administration (e.g. transdermal, oral or intramuscular) after starting GAHT in order to find a form that is easiest to use and produces minimal side effects, so future research could further examine whether different forms of GAHT have different effects on sleep.

There are a number of demographic factors we did not further explore in this study. Previous research has shown that subjective sleep quality and insomnia symptoms differ across age groups and with groups with lower or higher BMIs [64,65]. In our study we included mainly (young) adults, hence further research should investigate effects of GAHT on sleep in transgender adolescents and older transgender people to study whether these groups show different outcomes, either because of different forms of GAHT, as seen in adolescents using puberty suppressants, or because of longer endogenous hormone exposure and the effect of ageing, as seen in older GAHT users. However, as Participants' BMI also showed no confounding effects in our sample on the main outcomes variables. However, as the use of GAHT can increase BMI [66], future research should address whether participants who show strong changes in BMI after GAHT use are more at risk for poor sleep quality or sleep disorders such as insomnia or sleep apnea.

In summary, this study shows that transgender persons report poor sleep quality before GAHT, and that no clinically significant changes in insomnia or sleep quality occur after starting gender-affirming hormone use. However, there was a moderate reduction in sleep onset latency in trans women and marginal reduction sleep efficiency in trans men. Furthermore, we see that trans women who experience hot flashes report more insomnia symptoms than those who do not. Future studies on different hormone protocols, such as differences between CPA and GnRH analogs in trans women, could provide more insight into the underlying hormonal mechanisms affecting sleep quality. Considering the possible changes in sleep-wake duration after GAHT use, further studies should focus on the objective measurement of sleep during GAHT and on possible underlying mechanisms.

7. Data availability statement

Data available on request.

CRediT authorship contribution statement

Margot W.L. Morssinkhof: Conceptualization, Investigation, and, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Chantal M. Wiepjes:** Investigation, and, Data curation, Formal analysis, Writing – review & editing. **Breanna W. Bosman:** Conceptualization, Writing – original draft, Writing – review & editing. **Jim Kinds:** Conceptualization, Writing – original draft, Writing – review & editing. **Alessandra D. Fisher:** Investigation, and, Data curation, Writing – review & editing. **Yona Greenman:** Investigation, and, Data curation, Writing – review & editing. **Baudewijntje P.C. Kreukels:** Investigation, and, Data curation, Writing – review & editing. **Guy T'Sjoen:** Investigation, and, Data curation, Writing – review & editing. **Ysbrand D. van der Werf:** Conceptualization, Formal analysis, Writing – review & editing, Supervision. **Martin den Heijer:** Conceptualization, Formal analysis, Writing – review & editing, Supervision. **Birit F.P. Broekman:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing, Supervision.

Declaration of competing interest

The authors have no competing interests to declare. This work was supported by the NWO, Netherlands [Veni grant, grant number 91619085, 2018] supplied to BB. The NWO had no involvement in the study design, data collection, analysis or interpretation of the data, or writing of the report. All other authors have no financial conflicts of interest.

Acknowledgments

The authors would like to thank all ENIGI participants for their contributions to the study, and they would like to thank all the dedicated clinicians and researchers who contributed to the ENIGI study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2023.04.028.

References

[1] Hinz A, Glaesmer H, Brähler E, et al. Sleep quality in the general population: psychometric properties of the Pittsburgh Sleep Quality Index, derived from a German community sample of 9284 people. Sleep Med 2017;30:57–63. https://doi.org/10.1016/j.sleep.2016.03.008.
[2] Ammar A, Trabelsi K, Brach M, et al. Effects of home confinement on mental health and lifestyle behaviours during the COVID-19 outbreak: insights from the ECLB-COVID19 multicentre study. Biol Sport 2021;38(1):9–21. https://doi.org/10.5114/biolsport.2020.96857.
[3] Fatima Y, Doi S, Najman J. Exploring gender difference in sleep quality of young adults: findings from a large population study. Clin Med Res 2016;14. https://doi.org/10.3121/cmr.2016.1338.
[4] Wittchen HU, Jacobi F, Rehm J, et al. The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol 2011;21(9):655–79. https://doi.org/10.1016/j.euroneuro.2011.07.018.
[5] Morin CM, Jarrin DC. Epidemiology of insomnia: prevalence, course, risk factors, and public health burden. Sleep Med Clin 2022;17(2):173–91. https://doi.org/10.1016/j.jsmc.2022.03.003.
[6] Zeng LN, Zong QQ, Yang Y, et al. Gender difference in the prevalence of insomnia: a meta-analysis of observational studies. Front Psychiatr 2020:11.
[7] Lee SY, Ju YJ, Lee JE, et al. Factors associated with poor sleep quality in the Korean general population: providing information from the Korean version of the Pittsburgh Sleep Quality Index. J Affect Disord 2020;271:49–58. https://doi.org/10.1016/j.jad.2020.03.069.
[8] Li L, Sheehan CM, Thompson MS. Measurement invariance and sleep quality differences between men and women in the Pittsburgh sleep quality index. J Clin Sleep Med JCSM Off Publ Am Acad Sleep Med 2019;15(12):1769–76. https://doi.org/10.5664/jcsm.8082.

[9] Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB. Sex and depression in the national comorbidity survey I: lifetime prevalence, chronicity and recurrence. J Affect Disord 1993;29(2–3):85–96. https://doi.org/10.1016/0165-0327(93)90026-G.

[10] Venn S, Arber S, Meadows R, Hislop J. The fourth shift: exploring the gendered nature of sleep disruption among couples with children. Br J Sociol 2008;59(1):79–97. https://doi.org/10.1111/j.1468-4446.2007.00183.x.

[11] Hislop J, Arber S. Sleepers wake! The gendered nature of sleep disruption among mid-life women. Sociology 2003;37(4):695–711. https://doi.org/10.1177/00380385030374004.

[12] Zhang J, Chan NY, Lam SP, et al. Emergence of sex differences in insomnia symptoms in adolescents: a large-scale school-based study. Sleep 2016;39(8):1563–70. https://doi.org/10.5665/sleep.6022.

[13] Johnson EO, Roth T, Schultz L, Breslau N. Epidemiology of DSM-IV insomnia in adolescence: lifetime prevalence, chronicity, and an emergent gender difference. Pediatrics 2006;117(2). https://doi.org/10.1542/peds.2004-2629.

[14] Hashmi AM, Bhatia SK, Bhatia SK, Khawaja IS. Insomnia during pregnancy: diagnosis and rational interventions. Pakistan J Med Sci 2016;32(4):1030–7. https://doi.org/10.12669/pjms.324.10421.

[15] Ciano C, King TS, Wright RR, Perlis M, Sawyer AM. Longitudinal study of insomnia symptoms among women during perimenopause. J Obstet Gynecol Neonatal Nurs JOGNN 2017;46(6):804–13. https://doi.org/10.1016/j.jogn.2017.07.011.

[16] Leproult R, Van Cauter E. Effect of 1 week of sleep restriction on testosterone levels in young healthy men. JAMA, J Am Med Assoc 2011;305(21):2173–4. https://doi.org/10.1001/jama.2011.710.

[17] Ruge M, Skaaby T, Andersson AM, Linneberg A. Cross-sectional analysis of sleep hours and quality with sex hormones in men. Endocr Connect 2019;8(2):141–9. https://doi.org/10.1530/EC-18-0548.

[18] Auyeung TW, Kwok T, Leung J, et al. Sleep duration and disturbances were associated with testosterone level, muscle mass, and muscle strength–A cross-sectional study in 1274 older men. J Am Med Dir Assoc 2015;16(7):630.e1–6. https://doi.org/10.1016/j.jamda.2015.04.006.

[19] Ben Dor R, Harsh VL, Fortinsky P, Koziol DE, Rubinow DR, Schmidt PJ. Effects of pharmacologically induced hypogonadism on mood and behavior in healthy young women. Am J Psychiatr 2013;170(4):426–33. https://doi.org/10.1176/appi.ajp.2012.12010117.

[20] Bezerra AG, Andersen ML, Pires GN, et al. Hormonal contraceptive use and subjective sleep reports in women: an online survey. J Sleep Res 2020;29(6):e12983. https://doi.org/10.1111/jsr.12983.

[21] Morssinkhof MWL, Lamers F, Hoogendoorn AW, et al. Oral contraceptives, depressive and insomnia symptoms in adult women with and without depression. Psychoneuroendocrinology 2021;133:105390. https://doi.org/10.1016/j.psyneuen.2021.105390.

[22] Silva BH, Martinez D, Wender MCO. A randomized, controlled pilot trial of hormone therapy for menopausal insomnia - PubMed. Arch Womens Ment Health 2011;14(6):505–8. https://doi.org/10.1007/s00737-011-0242-2.

[23] Leibenluft E, Schmidt PJ, Turner EH, et al. Effects of leuprolide-induced hypogonadism and testosterone replacement on sleep, melatonin, and prolactin secretion in men. J Clin Endocrinol Metab 1997;82(10):3203–7. https://doi.org/10.1210/jcem.82.10.4270.

[24] Shigehara K, Konaka H, Sugimoto K, et al. Sleep disturbance as a clinical sign for severe hypogonadism: efficacy of testosterone replacement therapy on sleep disturbance among hypogonadal men without obstructive sleep apnea. Aging Male Off J Int Soc Study Aging Male 2018;21(2):99–105. https://doi.org/10.1080/13685538.2017.1378320.

[25] Liu PY, Yee B, Wishart SM, et al. The short-term effects of high-dose testosterone on sleep, breathing, and function in older men. J Clin Endocrinol Metab 2003;88(8):3605–13. https://doi.org/10.1210/jc.2003-030236.

[26] Morssinkhof MWL, van Wylick DW, Priester-Vink S, et al. Associations between sex hormones, sleep problems and depression: a systematic review. Neurosci Biobehav Rev 2020;118:669–80. https://doi.org/10.1016/j.neubiorev.2020.08.006.

[27] van Leerdam, Zajac JD, Cheung AS. The effect of gender-affirming hormones on gender dysphoria, quality of life, and psychological functioning in transgender individuals: a systematic review. Transgender Health 2023;8(1):6–21.

[28] Auer MK, Liedl A, Fuss J, et al. High impact of sleeping problems on quality of life in transgender individuals: a cross-sectional multicenter study. PLoS One 2017;12(2):e0171640. https://doi.org/10.1371/journal.pone.0171640.

[29] van Dijk D, Dekker MJHJ, Conemans EB, et al. Explorative prospective evaluation of short-term subjective effects of hormonal treatment in trans people—results from the European Network for the investigation of gender incongruence. J Sex Med 2019;16(8):1297–309. https://doi.org/10.1016/j.jsxm.2019.05.009.

[30] Dekker MJHJ, Wierckx K, Van Caenegem E, et al. A European Network for the investigation of gender incongruence: endocrine part. J Sex Med 2016;13(6):994–9. https://doi.org/10.1016/j.jsxm.2016.03.371.

[31] World Professional Association for Transgender Health. Standards of care for the health of transsexual, transgender, and gender nonconforming people. 2012 *[7th Version]*.

[32] Morssinkhof M. Effects of sex hormone use on sleep quality in the first year of transgender transition: an ENIGI study. https://doi.org/10.17605/OSF.IO/JSCPW.

[33] Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med 2001;2(4):297–307. https://doi.org/10.1016/S1389-9457(00)00065-4.

[34] Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatr Res 1989;28(2):193–213. https://doi.org/10.1016/0165-1781(89)90047-4.

[35] Morin CM, Belleville G, Bélanger L, Ivers H. The insomnia severity index: psychometric indicators to detect insomnia cases and evaluate treatment response. Sleep 2011;34(5):601–8. https://doi.org/10.1093/sleep/34.5.601.

[36] Manzar MD, Jahrami HA, Bahammam AS. Structural validity of the Insomnia Severity Index: a systematic review and meta-analysis. Sleep Med Rev 2021;60:101531. https://doi.org/10.1016/j.smrv.2021.101531.

[37] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. DSM-IV.; 1994.

[38] Heinemann K, Ruebig A, Potthoff P, et al. The Menopause Rating Scale (MRS) scale: a methodological review. Health Qual Life Outcome 2004;2:45. https://doi.org/10.1186/1477-7525-2-45.

[39] Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. J Stat Software 2015;67(1):1–48. https://doi.org/10.18637/jss.v067.i01.

[40] Kuznetsova A, Brockhoff PB, Christensen RHB. lmerTest package: tests in linear mixed effects models. J Stat Software 2017;83(13):1–26. https://doi.org/10.18637/jss.v082.i13.

[41] Ohayon M, Wickwire EM, Hirshkowitz M, et al. National Sleep Foundation's sleep quality recommendations: first report. Sleep Health 2017;3(1):6–19. https://doi.org/10.1016/j.sleh.2016.11.006.

[42] Kuhl H. Pharmacology of estrogens and progestogens: influence of different routes of administration. Climacteric J Int Menopause Soc 2005;8(Suppl 1):3–63. https://doi.org/10.1080/13697130500148875.

[43] Söderpalm AHV, Lindsey S, Purdy RH, Hauger R, De Wit H. Administration of progesterone produces mild sedative-like effects in men and women. Psychoneuroendocrinology 2004;29(3):339–54. https://doi.org/10.1016/S0306-4530(03)00033-7.

[44] Friess E, Tagaya H, Trachsel L, Holsboer F, Rupprecht R. Progesterone-induced changes in sleep in male subjects. Am J Physiol 1997;272(5 Pt 1):E885–91. https://doi.org/10.1152/ajpendo.1997.272.5.E885.

[45] Ohayon MM. Severe hot flashes are associated with chronic insomnia. Arch Intern Med 2006;166(12):1262–8. https://doi.org/10.1001/archinte.166.12.1262.

[46] Baker FC, Willoughby AR, Sassoon SA, Colrain IM, de Zambotti M. Insomnia in women approaching menopause: beyond perception. Psychoneuroendocrinology 2015;60:96–104. https://doi.org/10.1016/j.psyneuen.2015.06.005.

[47] Whiteman MK, Staropoli CA, Benedict JC, Borgeest C, Flaws JA. Risk factors for hot flashes in midlife women. J Womens Health 2003;12(5):459–72. https://doi.org/10.1089/154099903766651586.

[48] Nelson HD. Commonly used types of postmenopausal estrogen for treatment of hot flashes: scientific review. JAMA 2004;291(13):1610–20. https://doi.org/10.1001/jama.291.13.1610.

[49] Dosani M, Morris WJ, Tyldesley S, Pickles T. The relationship between hot flashes and testosterone recovery after 12 Months of androgen suppression for men with localised prostate cancer in the ASCENDE-RT trial. Clin Oncol R Coll Radiol G B 2017;29(10):696–701. https://doi.org/10.1016/j.clon.2017.06.009.

[50] Freedland SJ, Eastham J, Shore N. Androgen deprivation therapy and estrogen deficiency induced adverse effects in the treatment of prostate cancer. Prostate Cancer Prostatic Dis 2009;12(4):333–8. https://doi.org/10.1038/pcan.2009.35.

[51] Frisk J. Managing hot flushes in men after prostate cancer–a systematic review. Maturitas 2010;65(1):15–22. https://doi.org/10.1016/j.maturitas.2009.10.017.

[52] Fisher AD, Castellini G, Ristori J, et al. Cross-sex hormone treatment and psychobiological changes in transsexual persons: two-year follow-up data. J Clin Endocrinol Metab 2016;101(11):4260–9. https://doi.org/10.1210/jc.2016-1276.

[53] van Leerdam TR, Zajac JD, Cheung AS. The effect of gender-affirming hormones on gender dysphoria, quality of life, and psychological functioning in transgender individuals: a systematic review. Transgender Health. Published online September 6, 2021. doi:10.1089/trgh.2020.0094.

[54] Harry-Hernandez S, Reisner SL, Schrimshaw EW, et al. Gender dysphoria, mental health, and poor sleep health among transgender and gender nonbinary individuals: a qualitative study in New York city. Transgender Health 2020;5(1):59–68. https://doi.org/10.1089/trgh.2019.0007.

[55] Heylens G, Elaut E, Kreukels BPC, et al. Psychiatric characteristics in transsexual individuals: multicentre study in four European countries. Br J Psychiatry 2014;204(2):151–6. https://doi.org/10.1192/bjp.bp.112.121954.

[56] Valentine SE, Shipherd JC. A systematic review of social stress and mental health among transgender and gender non-conforming people in the United States. Clin Psychol Rev 2018;66:24–38. https://doi.org/10.1016/j.cpr.2018.03.003.

[57] Breslow AS, Brewster ME, Velez BL, Wong S, Geiger E, Soderstrom B. Resilience and collective action: exploring buffers against minority stress for transgender individuals. Psychol Sex Orientat Gend Divers 2015;2:253–65. https://doi.org/10.1037/sgd0000117.

[58] Baker FC, Maloney S, Driver HS. A comparison of subjective estimates of sleep with objective polysomnographic data in healthy men and women.

J Psychosom Res 1999;47(4):335–41. https://doi.org/10.1016/s0022-3999(99)00017-3.
[59] Ma Y, Goldstein MR, Davis RB, Yeh GY. Profile of subjective-objective sleep discrepancy in patients with insomnia and sleep apnea. J Clin Sleep Med JCSM Off Publ Am Acad Sleep Med 2021;17(11):2155–63. https://doi.org/10.5664/jcsm.9348.
[60] Della Monica C, Johnsen S, Atzori G, Groeger JA, Dijk DJ. Rapid eye movement sleep, sleep continuity and slow wave sleep as predictors of cognition, mood, and subjective sleep quality in healthy men and women, aged 20-84 years. Front Psychiatr 2018;9:255. https://doi.org/10.3389/fpsyt.2018.00255.
[61] Künzel HE, Murck H, Stalla GK, Steiger A. Changes in the sleep electroencephalogram (EEG) during male to female transgender therapy. Psychoneuroendocrinology 2011;36(7):1005–9. https://doi.org/10.1016/j.psyneuen.2010.12.014.
[62] Dolsen EA, Asarnow LD, Harvey AG. Insomnia as a transdiagnostic process in psychiatric disorders. Curr Psychiatr Rep 2014;16(9):471. https://doi.org/10.1007/s11920-014-0471-y.
[63] Hollander LE, Freeman EW, Sammela MD, Berlina JA, Grisso JA, Battistini M. Sleep quality, estradiol levels, and behavioral factors in late reproductive age women. Obstet Gynecol 2001;98(3):391–7. https://doi.org/10.1016/S0029-7844(01)01485-5.
[64] Chan WS, Levsen MP, McCrae CS. A meta-analysis of associations between obesity and insomnia diagnosis and symptoms. Sleep Med Rev 2018;40:170–82. https://doi.org/10.1016/j.smrv.2017.12.004.
[65] Stewart R, Besset A, Bebbington P, et al. Insomnia comorbidity and impact and hypnotic use by age group in a national survey population aged 16 to 74 years. Sleep 2006;29(11):1391–7. https://doi.org/10.1093/sleep/29.11.1391.
[66] Klaver M, Dekker MJHJ, de Mutsert R, Twisk JWR, den Heijer M. Cross-sex hormone therapy in transgender persons affects total body weight, body fat and lean body mass: a meta-analysis. Andrologia 2017;49(5):e12660. https://doi.org/10.1111/and.12660.