

TRANSGENDER HEALTH

Long-Term Gender-Affirming Hormone Therapy and Cognitive Functioning in Older Transgender Women Compared With Cisgender Women and Men



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ABSTRACT

Background: Long-term gender-affirming hormone therapy (GHT) in older transgender individuals could have beneficial effects on cognitive functioning. Cardiovascular risk factors and psychological factors are known determinants of cognition. Despite the rising number of older transgender individuals, only few studies have examined cognitive functioning in this population.

Aim: We aimed to assess differences in cognitive functioning between transgender women, and non-transgender (cisgender) women and men, and investigated the contribution of cardiovascular risk factors and psychological factors on these differences.

Methods: In this study, 37 transgender women (age range 55 to 69) receiving GHT for at least ten years (range 10.2 to 41.6) were examined, and their cognitive functioning was compared to an age and education level matched cohort consisting of 222 cisgender women and men from the Longitudinal Aging Study Amsterdam. Linear regression analyses were performed.

Outcomes: Cognitive functioning was assessed by neuropsychological tests including Mini-Mental State Examination (MMSE), Category Fluency animals, Letter Fluency D, 15-Word test (15WT) immediate and delayed recall. Additionally, cardiovascular risk factors and psychological factors such as cardiovascular disease, hypertension, antihypertensive use, statin use, diabetes mellitus, overweight, smoking, alcohol consumption, psychopharmaceutical use, anxiety and depression symptoms were collected.

Results: Transgender women had higher MMSE scores compared with cisgender women (+0.9, 95% CI 0.4 to 1.5), and cisgender men (+1.1, 95% CI 0.4 to 1.8). On all other tests transgender women performed similar to cisgender men. Transgender women performed at a lower level than cisgender women on 15WT immediate recall, -5.5, 95% CI -7.6 to -3.4, and 15WT delayed recall, -2.7, 95% CI -3.7 to -1.7, and equal to cisgender women on Fluency animals and Fluency D. Cardiovascular and psychological factors (i.e., cardiovascular disease and depression symptoms) partly explained differences on MMSE score between transgender women and cisgender-control groups.

Clinical Implications: The results of this study do not indicate a need for tailored hormone treatment strategies for older transgender women, based on cognitive aspects after long-term GHT.

Strengths & Limitations: As one of the first studies, this study compared older transgender women to a large cohort of cisgender men and women regarding cognitive functioning and took into account numerous potential influencing factors. Limitations include difference in test procedures and the cross-sectional design of the study.

Conclusion: Cognitive differences between transgender women and cisgender women and men were small, albeit significant. This may suggest that long-term GHT effects on cognitive functioning in older transgender

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Key Words: Gender Dysphoria; Older Transgender Women; Gender-Affirming Hormone Therapy; Cognitive Functioning; Cardiovascular Risk; Psychological Functioning

INTRODUCTION

Transgender women are individuals assigned male at birth identifying as female which may be accompanied with feelings of gender dysphoria. In cisgender (non-transgender) individuals, sex assigned at birth and gender identity align. Transgender women and transgender men (assigned female at birth, identifying as male) have the medical option to alleviate gender dysphoria by means of gender-affirming hormone therapy (GHT) and/or surgery. For transgender women, GHT consists of estrogen and, prior to potential orchiectomy, antiandrogen supplementation. For transgender men GHT consists of testosterone supplementation.¹ The health impact of (long-term) GHT on the growing population of older transgender individuals remains unclear.² Particularly, scientific literature addressing the influence of long-term GHT on cognitive functioning in older transgender women and transgender men is currently limited. Hormones affect cognitive functioning and can exert a potentially neuroprotective influence via androgen and estrogen receptors located in brain areas involved in cognitive functioning such as the hippocampus and the prefrontal cortex.^{3–6} The neuroprotective effect of estrogens has been observed in cisgender women and men.^{7–9}

Evidence regarding the possible result of these fundamental hormonal effects on cognition in the clinical setting largely stems from studies in cisgender women and men undergoing hormonal therapy or suppression. First, studies investigating cognition in patients that underwent hormonal therapy for prostate cancer found an overall, subtle negative effect of androgen deprivation on cognition (for review see ¹⁰). Second, anti-estrogenic treatment in breast cancer patients resulted, overall, in impaired cognitive functioning, particularly on verbal fluency tasks.^{11–15} Last, similar results were found in postmenopausal women: (post-)menopausal women performed less accurate on verbal fluency tasks than women in earlier reproductive stages,¹⁶ which correlated with sex-hormone concentrations.¹⁷ These findings provide information about effects of same-sex-hormone supplementation or deprivation on cognition and question what effect GHT has in transgender individuals.

In addition to effects of sex hormones, other parameters may affect cognitive functioning such as aging, social factors, pregnancy, lifestyle,³ and particularly cardiovascular and psychological factors; for example, hypertension and major depressive disorder are associated with cognitive impairment.^{18–19} Also,

associations were found between symptoms of depression and memory-function decline.²⁰ In addition, research suggests that transgender individuals have higher psychological vulnerability (e.g., higher rates of suicidal ideation, depression),²¹ particularly older transgender individuals (> 50 years) are at higher risk of experiencing stress and depression symptoms in comparison to cisgender individuals.²² The latter was associated with identity stigma.²³ Also, higher CVR (e.g., higher rates of venous thromboembolism, stroke and myocardial infarction) are found among the transgender population^{24–25} compared to cisgender individuals. For these reasons, it is important to also examine potential differences in CVR and psychological factors when comparing cognitive functioning between these groups.

Aim of this Study

Given the evidence above and the limited amount of information about the effect of GHT on older transgender individuals in the long-term, further investigation of cognitive functioning in this population is warranted.²⁶ In this study we only included transgender women because we did not have data available of transgender men. Therefore, we aimed to assess differences in cognitive functioning between older long-term GHT receiving transgender women recruited from the Center of Expertise on Gender Dysphoria and older cisgender men and women from the Longitudinal Aging Study Amsterdam (LASA) database.^{27–28} Furthermore, we investigated the contribution of cardiovascular risk factors and psychological factors on these differences. Based on previous research we hypothesized GHT to be associated with better cognitive performance (i.e., cognitive performance transgender women > cisgender women and men),^{3–17} and expected that differences in cognitive functioning would be partly explained by differences in CVR and psychological factors.^{18–21, 24–25}

MATERIAL AND METHODS

Participants

Forty-six older transgender women were recruited between 2008 and 2012 at the Center of Expertise on Gender Dysphoria at the Amsterdam University Medical Centers, location VU medical center. All were over 55 years of age, from different regions in the Netherlands, and had been receiving GHT for at least ten years. Clinical information from these subjects was

retrieved from the Amsterdam Cohort of Gender Dysphoria (ACOG) database.²⁹ Data from healthy Dutch cisgender men (N = 111) and cisgender women (N = 111) born between 1948 and 1957 (age range: 55–65) were obtained from the 2012–2013 wave of LASA – a nationally representative prospective cohort study in the Dutch older population (for details see Hoogendijk et al²⁷; Huisman et al²⁸). Five cisgender women (but no men) used hormone-replacement therapy (HRT). LASA participants were matched to the transgender women on age and education level. All participants gave written informed consent and approval was granted by the medical ethics review board of Amsterdam UMC, location VUmc.

Procedure

During their hospital visit the transgender women were neuropsychologically tested, filled out (mental health) questionnaires, and were medically screened for CVR. For the current study the following tests were used: (1) *Mini-Mental State Examination* (MMSE), (2) *Category Fluency Test* (“*Fluency animals*”), (3) *Letter Fluency Test* (“*Fluency D*”), and (4) Short form of the *15-Word Test* (15WT). The MMSE is a screening tool for memory problems and dementia (range 0–30).³⁰ The Dutch validated translation was used.³¹ For *Fluency animals* (part of the *Groninger Intelligentie Test*³²) and *Fluency D* (part of the Dutch equivalent of the *F-A-S test*³³) participants are asked to name as many animals, or words starting with a “d”, respectively, as possible in one minute. Both fluency tasks test memory and executive functioning. The 15WT is a measure of verbal memory which consists of 15 words that have to be memorized and recalled immediately in three trials (direct recall) and after approximately 20 minutes in a single trial (delayed recall). The Dutch validated version was used.³⁴ For a full description of this study’s entire test battery, see Schilder et al.³⁵

Mental health status was assessed using the *Hopkins Symptom Checklist-25* (HSCL-25) for current symptoms, which contains 15 depression and 10 anxiety items (higher scores indicate more symptoms; cut-off ≥ 1.75), and by information regarding psychopharmaceutical use for previous/continuing symptoms.

CVR screening included assessment of: hypertension (systolic ≥ 140 mmHg and/or diastolic ≥ 95 mmHg), antihypertensive medication use, statin use, body mass index (> 25 kg/m²), alcohol consumption ((i) no alcohol, (ii) ≤ 7 glasses and/or week, (iii) > 7 glasses and/or week), smoking (yes/no), diabetes mellitus, and history of cardiovascular disease (CVD, i.e., acute myocardial infarction, cerebrovascular accident, and vascular disease).

Similar information, mostly using identical tests, was gathered in the LASA study (for an overview of the complete study protocol, see Hoogendijk et al²⁷; Huisman et al²⁸), but this was collected in an ambulatory set-up. However, anxiety and depression symptoms were assessed using questionnaires different from those in transgender women: anxiety subscale of the *Hospital Anxiety Depression Scale* (HADS, range 0–21, cut-off > 7) and the *Center for Epidemiologic Studies Depression Scale* (CES-D, range

0–60, cut-off > 16), respectively. On both tests, higher scores indicate more symptoms. To increase the comparability of these measures with the sample of transgender women, we dichotomized the variables (clinically relevant and/or not clinically relevant symptoms), and compared sensitivity and specificity for the cut-off points used in this study.

Matching Variables

To every transgender woman (N = 37) three cisgender women and three cisgender men from the LASA database were matched based on age (matching range ≤ 5 years) and education level (matching range ≤ 1). Education level was divided in nine categories, which were recoded to the nominal number of years needed to complete the level of education (range 5–18 years). Matching (1:3) was determined based on sample size calculations with G*Power 3.0.10: effect size = 0.15 (medium), $\alpha = .05$, power = .95, number of predictors = 14 (i.e., 2 groups (transgender women vs. cisgender women; transgender women vs. cisgender men), 9 CVR factors, and 3 psychological factors), result: N = 194 participants.

Data Analysis

Three transgender women were excluded from the analyses due to missing cognitive data and six transgender women because they were older than 70 years and could therefore not be matched to cisgender controls. Descriptive statistics including GHT duration and percentage of individuals per group meeting the criteria for cardiovascular and/or psychological factors, were calculated separately per factor. Linear regression analyses were performed using SPSS 26.0 with Group (1. transgender women vs. cisgender women; 2. transgender women vs. cisgender men) as independent variable and cognitive performance (separately for all cognitive outcome measures; i.e., MMSE, Fluency animals, Fluency D, 15WT immediate and delayed recall) as dependent variable. After correction for multiple comparisons (ten main analyses), differences were considered to be significant at $\alpha = .005$ (.05/10). To examine to what extent group differences in cognitive performance were due to effects of cardiovascular and psychological factors, one factor per model was entered in hierarchical fashion to each main model as an independent predictor (i.e., CVD, hypertension, antihypertensive use, statin use, diabetes mellitus, overweight, smoking, light/heavy alcohol consumption, psychopharmaceutical use, anxiety and depression symptoms). The order of variables entered to the models was identical for all analyses. Results were considered significant if addition of a factor led to $\geq 10\%$ difference in the beta coefficient of the group dummy³⁶ and made a clinically significant difference. In case of multiple significant covariates, we added them simultaneously to a final model. Additionally, to control for sex-hormone exposure we conducted similar analyses with a subgroup of transgender women who were known to have adequately and consistently used GHT (N = 21) and cisgender women who did not use HRT (N = 96). Lastly, we examined

Table 1. Descriptive statistics of the included participants separately per group

| | Cis women | Trans women | Cis men |
|---|------------|-------------|------------|
| N | 111 | 37 | 111 |
| Age | 61.3 (2.9) | 62.3 (3.4) | 61.5 (2.7) |
| Age range | 56-65 | 55-69 | 56-65 |
| Education | 12.6 (3.5) | 12.4 (3.9) | 12.6 (3.5) |
| Education range | 6-18 | 6-18 | 6-18 |
| GHT duration | - | 24.3 (7.8) | - |
| GHT duration range | - | 11.2-41.6 | - |
| % HRT* | 4.5 | - | 0 |
| % Underwent gonadectomy | - | 100 | - |
| % Smoking | 11.7 | 40.5 | 20.7 |
| % No alcohol consumption | 14.4 | 29.7 | 9.9 |
| % Light alcohol consumption | 53.2 | 48.6 | 34.2 |
| % Heavy alcohol consumption | 32.4 | 21.6 | 55.9 |
| % Overweight (BMI>25kg/m ²) | 51.8 | 62.2 | 68.5 |
| % Hypertension | 41.4 | 50.0 | 54.1 |
| % Diabetes mellitus | 1.8 | 13.5 | 4.5 |
| % CVD | 3.6 | 18.9 | 9.0 |
| % Antihypertensives | 15.3 | 27.0 | 31.5 |
| % Statins | 12.6 | 19.4 | 21.6 |
| % Psychopharmaceutical use | 17.1 | 38.9 | 7.2 |
| % Anxiety symptoms | 15.3 | 11.8 | 7.2 |
| % Depression symptoms | 11.7 | 14.7 | 7.2 |

*Hormone-replacement therapy among cisgender women and men. Cis = cisgender; Trans = transgender; GHT = gender-affirming hormone therapy; CVD = history of cardiovascular disease. Data are presented as mean (SD), GHT duration and Education are displayed in years, % light alcohol consumption (1-7 glasses/week), % heavy alcohol consumption (>7 glasses/week).

the correlation between duration of GHT and cognitive performance within the group of transgender women.

RESULTS

Population Characteristics

The characteristics of the study population are shown in Table 1. On average, the transgender women had been receiving GHT for 24.3 years. Nine transgender women did not consistently and/or adequately use GHT for the following reasons: (i) GHT was stopped at least once before but was used at the time of testing (N = 4), (ii) estradiol dose was not adequate in multiple evaluations by a physician (N = 1), and/or (iii) GHT was already stopped for a while at the time of testing (N = 5). For seven transgender women information on consistency and/or adequacy of GHT use was missing. All had undergone gonadectomy. More transgender women (13.5%, 18.9%) had diabetes mellitus and/or cardiovascular disease, respectively, compared to cisgender women (1.8%, 3.6%) and cisgender men (4.5%, 9.0%). With regard to anxiety and depression symptoms, the percentage of transgender women (11.8%, 14.7%, respectively) was more similar to that of cisgender women (15.3%, 11.7% resp.) than to that of cisgender men (7.2%, 7.2% resp.). However,

considerably more transgender women (38.9%) (had) used psychopharmaceuticals compared to cisgender women (17.1%) and cisgender men (7.2%).

Differences in Cognitive Performance

Transgender women were more similar to cisgender men than to cisgender women regarding cognitive performance (Table 2, Figure 1). Transgender women differed significantly from cisgender women on MMSE and 15WT immediate and delayed recall. Scores were lower for transgender women on 15WT immediate and delayed recall, but they scored (slightly) higher on MMSE (difference +0.9, SE = 0.3, 95% CI 0.4 to 1.5, P = .001 (Table 2A, Figure 1). Transgender women differed significantly, albeit minimally, from cisgender men on MMSE score: scores were higher for transgender women than for cisgender men, difference +1.1, SE = 0.4, 95% CI 0.4 to 1.8, P = .003 (Table 2B, Figure 1). Transgender women did not perform differently from cisgender men on the other cognitive measures.

Cognitive performance was not associated with the duration of GHT in the group of transgender women for MMSE, $r = .12$, Fluency animals, $r = .16$, Fluency D, $r = -.04$, 15WT immediate recall, $r = -.16$, or for 15WT delayed recall, $r = -.05$.

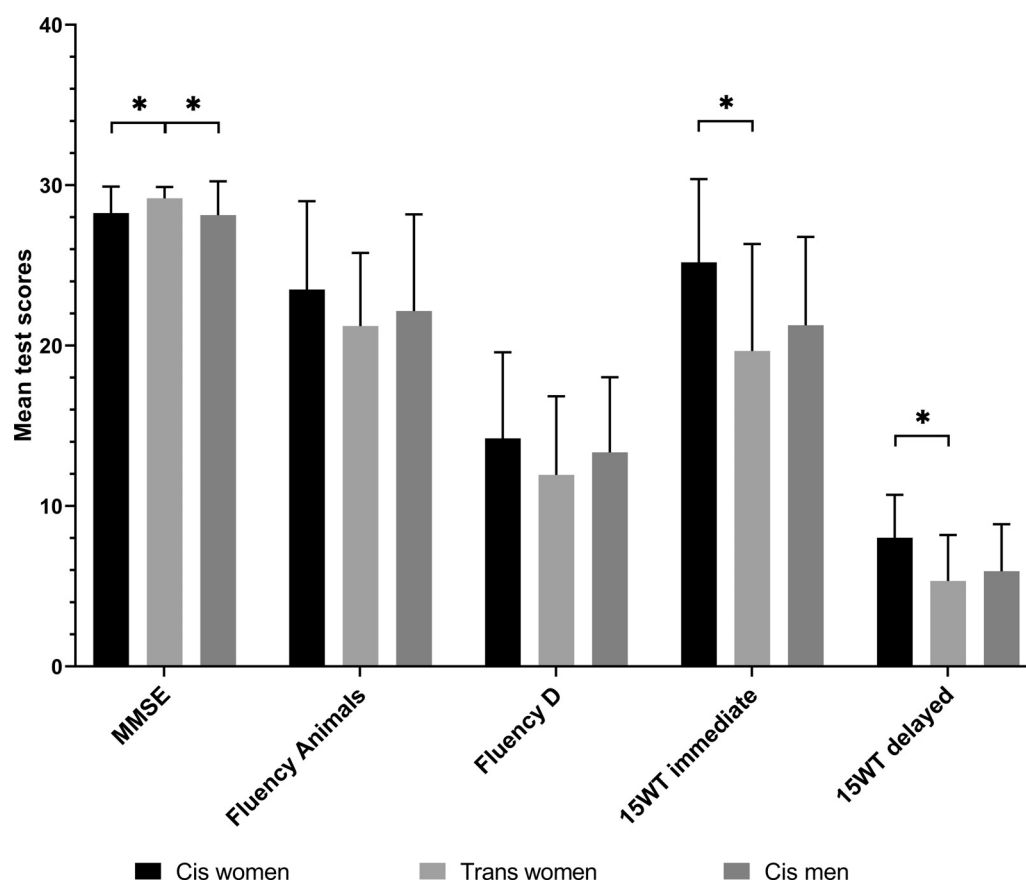


Figure 1. Cognitive performance in cisgender women, transgender women and cisgender men. Mean scores with standard deviations are shown on Mini-Mental State Examination (MMSE), Fluency animals, Fluency D, 15-Word test (15WT) immediate and delayed recall compared between transgender women and cisgender women, and between transgender women and cisgender men. *Significant based on $\alpha = .005$. Note that test scores are *not* presented as z-scores, therefore all tests have separate score ranges and *cannot* be compared to each other.

Effects of Cardiovascular and Psychological Factors

All tests for multicollinearity were negative: VIF well below 10 and tolerance well above 0.2.³⁷ Addition of CVD to the model that compared transgender women to cisgender women on MMSE score led to a 12.7% increase of the beta coefficient, making the difference between the groups larger (Table 2A). No other cardiovascular or psychological factors explained the differences on MMSE, nor did any factor explain differences on Fluency animals, Fluency D, 15WT immediate or delayed recall.

The difference between transgender women and cisgender men on MMSE score increased with 11.1% when depression symptoms were added (Table 2B). This difference increased with 26.2% when alcohol consumption was (separately) added (Table 2B). Light and heavy alcohol consumption similarly contributed to this effect, $part = .18$ and $.21$ respectively. Combined addition of alcohol consumption and depression symptoms to this model increased the beta coefficient with 29.6%. No (other) factors explained differences between the groups on the cognitive outcome measures.

Subgroup Analyses

Since nine transgender women did not consistently and/or adequately use GHT, information about this was missing for seven transgender women, and five cisgender women received HRT we conducted additional regression analyses with data of the transgender women who adequately and consistently used GHT ($N = 21$) and cisgender women that did not use HRT ($N = 96$). For the comparison between transgender women and cisgender women, results were similar to that of the main analyses. Addition of depression symptoms to the model comparing transgender women to cisgender men on MMSE score did not result in a 10% difference in beta coefficient. All other results were similar to the main analyses.

DISCUSSION

The aim of this study was to assess differences in cognitive functioning between transgender women using GHT, cisgender

Table 2. Summary of main linear regression analyses between Group (A, B) and cognitive outcome measures (1-5), and secondary models with significantly contributing cardiovascular and psychological factors

| | <i>B (SE)</i> | <i>95% CI</i> | <i>p</i> | <i>R²/ ΔR²</i> | <i>Part</i> | <i>ΔB (%)</i> |
|---|---------------|---------------|----------|--------------------------------------|-------------|---------------|
| A. Transgender women vs. cisgender women | | | | | | |
| 1A. Main model – MMSE | | | | .07 | | |
| Group | 0.9 (0.3) | 0.4 – 1.5 | .001* | | | |
| 1B. Contributing factor | | | | .02 | | 12.7 |
| Group | 1.0 (0.3) | 0.5 – 1.6 | <.001 | | | |
| Cardiovascular disease | -0.8 (0.5) | -1.7 – 0.2 | .108 | | -.13 | |
| 2A. Main model – Fluency Animals | | | | .03 | | |
| Group | -2.3 (1.0) | -4.3 – -0.3 | .025 | | | |
| 3A. Main model – Fluency D | | | | .03 | | |
| Group | -2.3 (1.0) | -4.3 – -0.3 | .027 | | | |
| 4A. Main model – 15WTimm | | | | .16 | | |
| Group | -5.5 (1.1) | -7.6 – -3.4 | <.001* | | | |
| 5A. Main model – 15WTdel | | | | .15 | | |
| Group | -2.7 (0.5) | -3.7 – -1.7 | <.001* | | | |
| B. Transgender women vs. cisgender men | | | | | | |
| 1A. Main model – MMSE | | | | .06 | | |
| Group | 1.1 (0.4) | 0.4 – 1.8 | .003* | | | |
| 1B. Contributing factors | | | | .05 | | 26.2 |
| Group | 1.3 (0.4) | 0.6 – 2.1 | <.001 | | | |
| Alcohol – light | 1.1 (0.5) | 0.1 – 2.0 | .024 | | .18 | |
| Alcohol – heavy | 1.3 (0.5) | 0.3 – 2.2 | .008 | | .21 | |
| 1B. Contributing factors | | | | .06 | | 11.1 |
| Group | 1.2 (0.4) | 0.5 – 2.0 | .001 | | | |
| Depression symptoms | -1.6 (0.5) | -2.7 – -0.6 | .003 | | -.24 | |
| 1C. Factors combined | | | | .09 | | 29.6 |
| Group | 1.4 (0.4) | 0.7 – 2.2 | <.001 | | | |
| Alcohol – light | 0.9 (0.5) | -0.0 – 1.9 | .061 | | .15 | |
| Alcohol – heavy | 1.1 (0.5) | 0.2 – 2.1 | .022 | | .18 | |
| Depression symptoms | -1.5 (0.5) | -2.5 – -0.4 | .006 | | -.22 | |
| 2A. Main model – Fluency Animals | | | | .01 | | |
| Group | -0.9 (1.1) | -3.1 – 1.2 | .384 | | | |
| 3A. Main model – Fluency D | | | | .02 | | |
| Group | -1.4 (0.9) | -3.2 – 0.4 | .127 | | | |
| 4A. Main model – 15WTimm | | | | .01 | | |
| Group | -1.6 (1.1) | -3.8 – 0.6 | .152 | | | |
| 5A. Main model – 15WTdel | | | | .01 | | |
| Group | -0.6 (0.6) | -1.7 – 0.5 | .290 | | | |

*Significant based on $\alpha = .005$. MMSE = mini-mental state examination; 15WTimm = 15-word test immediate recall; 15WTdel = 15-word test delayed recall. One cardiovascular or psychological factor per model was entered in hierarchical fashion to each main model (models 1a-5a). Only results from models in which factors led to substantial change in the coefficient of Group ($\Delta B \geq 10\%$) are shown (referred to as models b), and combined in one model if this was true for >1 factor (referred to as models c). R^2 is presented for a, ΔR^2 is presented for b and c, $\Delta B = \%$ difference between beta coefficients of the Group dummy in a and b/c, Alcohol – light = 1-7 glasses/week, Alcohol – heavy = >7 glasses/week.

women, and cisgender men. Transgender women were found to be more similar to cisgender men than to cisgender women in cognitive functioning profile. Contrary to our expectations and previous research showing that sex-hormone exposure was associated with a more favorable cognitive profile,⁷⁻¹⁷ transgender women did not consistently perform better than cisgender women and men on the neuropsychological tests, except slightly better on MMSE. Additionally, adjusting for sex-hormone

exposure in the subgroup analyses by only including transgender women with confirmed consistent and adequate use of GHT and cisgender women not using HRT, did not change results. Moreover, we found no significant correlations between duration of GHT and cognitive functioning. Importantly, no indications of adverse cognitive effects of long-term GHT were found in the group of transgender women included in this study when cisgender men are taken as the reference group.

Furthermore, in this study we aimed to investigate the contribution of CVR and psychological factors on the differences found in cognitive functioning. We found that the addition of CVD led to an increase of the difference between transgender women and cisgender women on MMSE score in favor of transgender women. Since more transgender women had CVD, this is in line with our expectations and previous research showing CVD to be a risk factor for cognitive impairment.¹⁸ In other words, if CVD would have been equal in transgender and cisgender women, the transgender women would have performed even better on MMSE, i.e., CVD seemed to have a suppressive effect on MMSE score. The difference between transgender women and cisgender men on MMSE score increased in favor of transgender women when adjusted for depression symptoms which were more common among transgender women than cisgender men. This is in line with previous research suggesting depression to be a risk factor for cognitive decline.¹⁹⁻²⁰ However, this effect was not present anymore in the subgroup analysis which suggests that GHT might influence the association between depression and cognitive functioning. It is argued that estradiol is negatively associated with depression in older cisgender women.⁶ What this means for GHT in (older) transgender women is not yet known. Lastly, adjusting for alcohol consumption in the comparison between transgender women and cisgender men on MMSE score resulted in a bigger difference between the groups in favor of transgender women. Since fewer transgender women consumed alcohol compared to cisgender men, this result is against expectations and not in line with previous research showing a negative association between alcohol consumption and cognitive domains such as memory and executive functioning.³⁸⁻³⁹ Because we cannot explain this paradoxical finding (possibly due to reporting bias or underlying medical issues and/or medication use as a reason for not consuming alcohol) future research should further explore alcohol consumption and its contribution to cognitive functioning.

In summary, minimal cognitive differences were found between transgender women and cisgender men which were partly associated with depression symptoms and alcohol consumption. Transgender and cisgender women differed on MMSE, which was associated with CVD, and both 15WT tasks. Whether these CVR and psychological factors are mediating or confounding factors of the relationship between group and cognitive functioning remains unclear since no inferences about direction of effects can be made based on the cross-sectional study-design.

The greater cognitive similarity between transgender women and cisgender men is consistent with studies showing no difference in cognitive performance between transgender women receiving GHT and control cisgender men.⁴⁰⁻⁴¹ However, a study by van Goozen and colleagues showed improved verbal fluency (a supposedly female-favoring cognitive domain) and decreased performance on a visuospatial task (supposedly male-favoring) in transgender women after receiving GHT for three

months.⁴² In contrast, in the current study transgender women scored equal to or lower than cisgender women on the female-favoring domains (assessed with Fluency and 15WT tasks), and (slightly) higher on MMSE which also includes male-favoring tasks. Though, it must be mentioned that the transgender women included in the study by van Goozen were significantly younger (*mean age* = 32.4 years) than the transgender women in the current study (*mean age* = 62.3 years). A possible explanation for this contradictory finding and, in general, the lack of superior cognitive performance in the transgender women compared with the cisgender women and men could be the inconsistent hormone use among several transgender women in this study: 21 transgender women consistently used GHT, whereas nine did not consistently use GHT and this information was missing for seven. However, analyses in transgender women with adequate GHT use (and exclusion of cisgender women using HRT) showed no difference in results compared to the main analyses and no significant correlations were found between duration of GHT and cognitive functioning. However, all transgender women had switched route of estradiol administration at least once during their treatment period. This could have influenced cognitive performance, since previous research has suggested that distinct routes of estradiol administration differentially affect cognitive functioning.⁴³ Another explanation for the lack of superior cognitive performance in the transgender women compared with the cisgender women and men could be that estradiol might only prevent cognitive impairment but that administration of estradiol does not actively improve cognitive functioning. This is supported by previous research showing that estrogen therapy did not improve cognitive functioning in individuals with Alzheimer's disease but did decrease risk of developing dementia in postmenopausal women.⁴⁴⁻⁴⁵ However, it is theorized that this is dependent on the timing of hormone-therapy initiation. Lastly, due to the relatively young sample differences in the speed of cognitive decline may not (yet) be visible.

Strengths and Limitations

As one of the first studies, this study compared older transgender women to a large cohort of cisgender men and women regarding cognitive functioning and took into account numerous potential influencing factors. Furthermore, despite of limited availability of identical data in the trans- and cisgender groups, we were able to collect test scores on multiple cognitive domains. However, the results of this study should be seen in light of several limitations. First, due to the cross-sectional study design, our results are merely descriptive. Second, testing procedures of the transgender women and cisgender women and men were not entirely identical. LASA data was gathered in the home environment and used for research purposes only, whereas transgender women were tested in a clinical setting, partly during their routine clinical check-up. This raises the possibility of reporting bias on lifestyle factors such as smoking and alcohol consumption: research shows clinically desirable reporting of lifestyle factors (e.

g., underreporting of alcohol consumption) in treatment settings due to a perceived pressure to answer in a (clinically) desirable way.⁴⁶ Additionally, not all factors, such as anxiety and depression, were assessed using identical questionnaires. Therefore, all potential mediators and/or confounders were dichotomized and their cut-off points were compared regarding validity based on previous studies: the *HSCL-25* had a sensitivity and a specificity of 94%,⁴⁷ the *HADS* anxiety subscale a sensitivity of 73% and a specificity of 65%,⁴⁸ and the *CES-D* had a sensitivity of 87% and a specificity of 70%.⁴⁹ Because validity of these instruments is not identical, results regarding psychological symptoms should be interpreted with caution. Lastly, multiple factors not available in this study's datasets such as lifestyle and social factors may impact cognitive functioning as well.³ Therefore, further study of other factors that may impact cognitive functioning is warranted.

Recommendations for Future Research

For future research, it is recommended to test older transgender women, transgender men, cisgender women, and cisgender men using a more comprehensive and identical cognitive-test battery and psychological screening. Of great importance is the inclusion of a homogenous group of transgender participants with regard to GHT (i.e., similar formulations and doses), or a sufficient sample size to control for this. A longitudinal-study design with multiple measurements in time would greatly contribute to answers regarding the direction of effects. In addition, it would be of great value to include older transgender women *not* receiving and/or about to start GHT to serve as an extra control group, thereby controlling for the difference between transgender and cisgender individuals in the experience of gender dysphoria and other potential differences between these groups. A greater sample size and more extensive matching could also make the groups more comparable.

We want to further stress the importance of future research on this topic since older transgender individuals are an especially vulnerable group: They are at higher risk of experiencing stress and depression symptoms compared to cisgender individuals,²² report higher rates of subjective cognitive decline (particularly those also reporting depression symptoms),⁵⁰ have more risk factors linked to cognitive impairment such as social isolation and chronic illness, and experience more barriers to access health care.⁵¹ Therefore, it is crucial to further assess cognitive functioning in older transgender individuals while addressing the numerous social, psychological and medical challenges this group faces.

CONCLUSIONS

The number of (older) transgender individuals receiving GHT is rising, although the long-term impact on an individual's health has remained largely unclear.² The data collection at the Center of Expertise on Gender Dysphoria and LASA has given us a unique opportunity to address this underattended topic. To

the best of our knowledge, this is one of the first studies investigating (cognition in) older transgender women. Numerous important factors interacting with cognition were taken into account. Cognitive differences between transgender women and cisgender women and men were small, albeit significant, therefore these results might indicate that long-term GHT effects on cognitive functioning in older transgender women are minimal. This may suggest that transgender women are protected against cognitive decline, because they did show greater cardiovascular and psychological challenges.

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