


Cognitive functioning in older transgender individuals receiving long-term gender-affirming hormone therapy

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ABSTRACT

Background: Cognitive functioning can be negatively influenced by age, cardiovascular risk (CVR) and mental health challenges, and sex-hormones can have neuroprotective effects. Little is known about cognitive functioning in older transgender individuals receiving long-term gender-affirming hormone therapy (GHT). In a previous, smaller study, cognitive differences between transgender women and cisgender groups were minimal yet statistically significant.

Aims: This study assessed cognitive differences between larger samples of older transgender and cisgender individuals, and the contribution of CVR and mental/social health to these differences.

Methods: This cross-sectional study compared 73 transgender women and 39 transgender men (56–84y) receiving long-term GHT (10–47y) with matched (age; education level) cisgender women and men from the Longitudinal Aging Study Amsterdam on cognitive functioning assessed with neuropsychological tests. Mean z-scores per cognitive domain were calculated and analyzed using linear regression. Models were subsequently adjusted for CVR ((history of) cardiovascular disease; smoking) and mental/social health (anxiety; loneliness) factors.

Results: Transgender women had lower scores than cisgender women and men, respectively, on information-processing speed ($b = -0.62$, 95% CI -0.90 to -0.35 ; $b = -0.33$, 95% CI -0.60 to -0.05), episodic memory ($b = -1.28$, 95% CI -1.53 to -1.04 ; $b = -0.77$, 95% CI -1.01 to -0.52), and crystallized intelligence ($b = -0.42$, 95% CI -0.75 to -0.10 ; $b = -0.41$, 95% CI -0.75 to -0.08). Transgender men scored lower on episodic memory than cisgender women but scored equal to cisgender men ($b = -0.43$, 95% CI -0.79 to -0.08 ; $b = -0.01$, 95% CI -0.36 to 0.35). Mental/social health factors (particularly depressive symptoms) largely, and CVR factors slightly, explained cognitive differences between the trans- and cisgender groups.

Discussion: Small cognitive differences between transgender men and cisgender groups do not suggest adverse or beneficial long-term testosterone effects on cognitive functioning. However, transgender women had lower cognitive functioning than cisgender groups, which was largely explained by mental/social health. This warrants further research and clinical awareness of mental and cognitive health in older transgender individuals.

KEYWORDS

Aging; cardiovascular risk; episodic memory; estradiol therapy; mental and social health; testosterone therapy

Introduction

Although long-term outcomes of care for transgender individuals are gaining increasing attention, a general lack of information *and* clinical guidelines regarding gender-affirming hormone therapy (GHT) in older transgender individuals remains (Coleman et al., 2022; den Heijer et al.,

2017; Hembree et al., 2017; Libby et al., 2019). In particular, the impact of long-term GHT on various mental and physical health outcomes is unclear (Feldman et al., 2016; van Heesewijk et al., 2021). Impaired cognitive functioning is associated with negative outcomes on several aspects of life such as depression, loneliness,

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barriers in seeking mental or physical healthcare, and ultimately a lower quality of life (Comijs et al., 2005). Impaired cognitive functioning is common among older individuals (16.8–26.6%) and with the growing older (cis- and transgender) population, this is an important issue (Graham et al., 1997; Hanninen et al., 1996; Ritchie et al., 2001; Schroder et al., 1998; Unverzagt et al., 2001).

Cognitive functioning can be influenced by sex hormones, as is predominantly known from studies in postmenopausal women receiving hormone replacement therapy (HRT) and studies in prostate- and breast-cancer patients. Woolie et al. (2015) randomized cognitively healthy postmenopausal women (age 49–69 y) with increased Alzheimer's Disease risk using HRT (either 17 β -estradiol or conjugated equine estrogen (CEE)) to continue or stop treatment for two years. Most women started HRT early in menopause. Stopping HRT led to lower scores on multiple cognitive domains, such as verbal memory and women continuing HRT showed a slight increase in verbal memory (although this might be due to practice effects). However, other randomized-controlled trials did not show differences in cognitive functioning after starting 17 β -estradiol (Almeida et al., 2006) and CEE + medroxyprogesterone acetate (Binder et al., 2001) in a sample of older women (>70 y and >75 y, respectively). Of note, the follow-up time was shorter (<9 months) and the mean age (of HRT initiation) was higher in these studies. Furthermore, studies investigating cognitive functioning after anti-estrogenic treatment for breast cancer showed more cognitive impairment, specifically on verbal fluency (Collins et al., 2009; Jenkins et al., 2004; Lee et al., 2016; Shilling et al., 2003; Zwart et al., 2015). Studies in prostate-cancer patients showed slightly lower cognitive functioning after androgen deprivation (which might also be due to estrogen deprivation as a result of less aromatization) (Yeap, 2014). These results suggest a direct neuroprotective effect of sex hormones in (cisgender) women and men, which could be neurobiologically explained by the presence of estrogen and androgen receptors in, among others, the prefrontal cortex and hippocampus, which are involved in cognitive

functioning (Ali et al., 2018; Arevalo et al., 2015; Azcoitia et al., 2011; Janicki & Schupf, 2010; Navarro-Pardo et al., 2017; Siddiqui et al., 2016).

Whether these findings can be extrapolated to GHT's influence on cognitive functioning in transgender individuals is unknown. However, (limited) information on the prevalence of dementia, subjective cognitive decline, and cognitive functioning in transgender compared to cisgender individuals is available. In the United States, more transgender individuals have a dementia diagnosis compared to cisgender individuals based on ICD codes and health insurance data (Guo et al., 2022; Hughto et al., 2023). Also, older (45+) transgender individuals in the U.S., particularly of ethnic minorities, and individuals part of sexual and gender minorities (SGM), more frequently reported increased confusion or memory loss in the past year compared to cisgender and non-SGM individuals, respectively (Cicero et al., 2023; Flatt et al., 2021). Recently, we conducted a study comparing cognitive functioning in older transgender women (>55 y) receiving long-term GHT (estrogens only) to older cisgender men and women (van Heesewijk et al., 2021). Transgender women performed statistically better on general cognitive function compared to cisgender women and men but lower on verbal memory compared to cisgender women.

In addition to an influence of sex hormones on cognitive functioning, mental and physical health aspects such as depression and hypertension are known to be associated with cognitive impairment (Brailean et al., 2017; Gorelick, 2018; Knight & Baune, 2018). Also, (older) transgender individuals have more mental health challenges and a higher cardiovascular risk (CVR) compared to the general population (Fredriksen-Goldsen et al., 2014; Getahun et al., 2018; Hoy-Ellis et al., 2017; Irwig, 2018; Nota et al., 2019). Hence, these factors are important to consider when studying cognitive functioning in transgender individuals. Therefore, in this study, we aimed to assess cognitive functioning differences between older transgender women and men receiving long-term GHT and cisgender women and men of similar age, and to study the contribution of mental and social health (further referred to as

mental health) and CVR factors to differences in cognitive functioning between the groups.

Materials and methods

Participants and matching

Eighty transgender men and 172 transgender women were invited to participate by the Center of Expertise on Gender Dysphoria (CEGD) at the Amsterdam University Medical Centers, location VUmc in 2021 of which 21 could not be reached, four were deceased, eight did not participate for health reasons, of which three had neurological morbidity, and the remainder ($N=107$) for unknown or other reasons such as no current GHT use ($N=4$), no time ($N=15$), or having left behind their transition ($N=7$). Seventy-three transgender women and 39 transgender men participated, of which four women had also participated in a previous study (van Heesewijk et al., 2021). Inclusion criteria were an age of 55 years or older, receiving GHT for at least 10 years, and regular endocrine follow-up visits at the CEGD at the time of participation (i.e. last clinical appointment <3 years ago). Participants lived in various regions in the Netherlands. Those who had an insufficient understanding of the Dutch language were excluded from the study ($N=1$). Using a cross-sectional design, these participants were compared to older cisgender women and men from the Longitudinal Aging Study Amsterdam (LASA) database, a prospective cohort study representative of the general older Dutch population (for details, see Hoogendijk et al., 2020; Huisman et al., 2011). Data of cisgender participants were collected between 2015 and 2016 (termed LASA wave I) and consisted of three cohorts with birth years between 1908 and 1957.

Cisgender women and men ($N=219$ for transgender women, $N=117$ for transgender men) were separately matched 1:3 on age and education level to transgender women and men (see Figure A1 in Appendix for an overview of the matching process). First, cisgender participants were matched to transgender women, and then matches for transgender men (smaller sample needed due to the smaller number of transgender men) were retrieved from the cisgender pool

matched to the transgender women. Matching range for age was ≤ 5 years, and for education level was ≤ 2 categories. Education level consisted of nine categories.¹ Matching 1:3 was chosen based on a priori G*Power 3.0.10 sample size calculations: $\alpha = .05$, effect size = 0.15, power = .95, predictor no. = 11 (group (transgender women vs. cisgender men or women, or transgender men vs. cisgender men or women), 6 CVR factors, 4 mental health factors), result: $N=178$. Written informed consent was given by all participants, and the medical ethics review board of Amsterdam UMC, location VUmc granted approval (NL72669.029.20).

Procedure and variables

This study is part of a larger project on health outcomes in older transgender individuals, for which all participants were interviewed by LASA interviewers using identical protocols: A face-to-face interview was conducted in the participant's home environment (or if a home visit was not possible or inconvenient at Amsterdam UMC), and participants were asked to fill out a questionnaire after the interview (Hoogendijk et al., 2020; Huisman et al., 2011). During the interview, information on demographics, cognitive functioning, physical and mental health, lifestyle, loneliness, mastery, and discrimination was collected. The self-report questionnaire focused on satisfaction with life, sleep quality, gender identity and gender affirming treatment, body image, sexuality, and self-perceived health questions. Endpoints of particular interest for this study include cognitive functioning, mental health, and cardiovascular factors.

Cognitive functioning

The following neuropsychological tests were included: Coding task, 15-Word test immediate and delayed recall, Letter Fluency (D), Category Fluency (animals), Digit span forward and backward, Vocabulary test, and Mini-Mental State Examination (MMSE). For the MMSE, the validated Dutch translation was used as a screening tool (not as an outcome measure) for potentially serious cognitive impairment for sensitivity

analyses (range 0–30, cutoff for serious cognitive impairment <24) (Folstein et al., 1975; Kok & Verhey, 2002). The Coding task is an adjusted version of the Alphabet Coding Task-15 which measures *information processing speed* and is sensitive to aging (Salthouse, 1996; Savage, 1984). In three one-minute trials, participants have to name (instead of write down, to avoid dependence of the score on motor speed) as many characters as possible corresponding to specific letters as indicated at the top of the test (outcome: mean score of three trials, range: 1–42.7) (Piccinin & Rabbitt, 1999). The 15-Word test is the Dutch validated version of the Auditory Verbal Learning Test which measures (*verbal episodic memory*) and is associated with age, sex and education (Rey, 1964). A short version was used for which participants had to memorize and recall 15 words in three trials (instead of the usual five trials) (i.e. immediate recall, outcome: total correct of three trials, range: 0–45) and recall after 20–30 min (i.e. delayed recall, outcome: total correct, range: 0–15) (van den Burg et al., 1985). *Executive functioning* was measured with a Letter Fluency (Dutch equivalent) and Category Fluency task in which participants had to name as many words starting with “D” (Spreeen, 1977) and as many animals as possible (Luteijn & Barelds, 2004), respectively, in one minute (outcomes: words total, range: 0–∞). The Digit span tasks are part of the Wechsler Adult Intelligence Scale IV and also measure executive functioning (Wechsler, 1958). Participants had to recall an increasing number of digits forward (i.e. Digit span forward, outcome: total correct, range: 0–16) and backward (i.e. Digit span backward, outcome: total correct, range: 0–14). These tests assessing executive functioning are age-sensitive (Drag & Bieliauskas, 2010). The Vocabulary test that is part of the Groninger Intelligence test, measures *crystallized intelligence* and typically remains stable with age (Luteijn & Barelds, 2004). Participants had to choose a synonym from a list of five for 20 increasingly difficult words (outcome: total correct, range: 0–20). Higher scores on all tests indicate better cognitive functioning. Lastly, participants were asked to subjectively report on memory problems (yes/no).

Mental and social health factors

Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression Scale (CES-D), a self-report scale consisting of 20 items about depressive symptoms in the past week (outcome: total score, range: 0–60) (Radloff, 1977). Anxiety symptoms were assessed with the Hospital Anxiety Depression Scale anxiety subscale (HADS-A), which measures self-reported anxiety symptoms on seven items in the past four weeks (outcome: total score, range: 0–21) (Zigmond & Snaith, 1983). Loneliness was measured with the De Jong-Gierveld Loneliness Scale, an 11-item self-report scale (outcome: total score, range: 0–11) (De Jong-Gierveld & Kamphuls, 1985). For all scales, higher scores indicate more symptoms/loneliness. Lastly, recent mental health care such as hospitalization or a psychiatrist/psychologist visit in the past six months (yes/no) was included.

Cardiovascular factors

The following CVR factors were collected: (History of) cardiovascular disease (acute myocardial infarction, vascular disease, and/or cerebrovascular accident), diabetes (yes/no), Body Mass Index (BMI in kg/m²), hypertension (yes/no based on mean systolic ≥ 140 mmHg and/or mean diastolic blood pressure ≥ 95 mmHg and/or antihypertensive use), and lifestyle, including current smoking (yes/no) and alcohol consumption (no consumption, or light to very excessive; see Table A1 in Appendix).

Transgender specific factors

For transgender participants, additional clinical data, including GHT duration (years), gonadectomy (yes/no), and height (meters), were collected using the database of the Amsterdam Cohort of Gender Dysphoria (ACOG) (Wiepjes et al., 2018). To explain cognitive differences between transgender women and cisgender groups, mean 17-beta-estradiol levels (pmol/l) over the years per transgender woman were secondarily collected.

Data analyses

The data of one transgender woman were excluded from all analyses because of being illiterate (mentioned by participant during testing), data of one

cisgender man were excluded from analyses due to a lack of test scores for an unknown reason, and data from one cisgender woman were not used because her MMSE score was an outlier (>3 IQR) and all other test scores were low. Participants with incidental missing data on some tests were only excluded from those analyses (% missing $< 3\%$). For the Vocabulary test, only baseline scores were collected by LASA since these remain stable in older age (LASA, 2019). Therefore, data were only available for the most recent cisgender cohort (139 cisgender men; 145 women).

Descriptive statistics were calculated per group, including baseline clinical data such as GHT duration, HRT use, gonadectomy status for transgender participants, percentage of individuals per group with a deviant MMSE score (<24), meeting the criteria for cardiovascular risk factors, and average scores on mental health questionnaires. Cognitive functioning tests were divided into four groups based on the cognitive domains assessed: 1) information processing speed (coding task), 2) episodic memory (15-word test: immediate and delayed recall), 3) executive functioning (letter and category fluency, digit span: forward and backward), and 4) crystallized intelligence (vocabulary test) (Bouma et al., 2012; Hoogendijk et al., 2020). Mean z-scores were calculated per cognitive domain using the mean and standard deviation of the cisgender control group as a reference. Z-scores of individual tests within cognitive domains were checked for similarity of (direction of) results.

To compare group differences on cognitive outcome measures, linear regression analyses were performed using Stata/SE 15.1 with Group (1. transgender women vs. cisgender women, 2. transgender women vs. cisgender men, 3. transgender men vs. cisgender women, and 4. transgender men vs. cisgender men) as independent variable and cognitive performance (separately per domain) as dependent variable. Due to missing cisgender data on the Vocabulary test, these models were corrected for age and education level. Relevant group differences were identified based on 95% confidence intervals, and effect size/clinical relevance (as assessed by a clinical neuropsychologist (GG)). Group differences on subjective report of memory problems were analyzed with logistic regression analyses.

Models were subsequently adjusted for cardiovascular and mental health factors by clustered addition of these factors to the main model (in identical order for all analyses), leading to four models per group comparison: A) Main model, B) model including all CVR factors, C) model including all mental health factors, and D) overall model with all CVR and mental health factors. The clustered factors in models B–D were considered substantial when leading to $>10\%$ and relevant differences (>0.1 z-score) in the group-dummy regression coefficient (Hernan et al., 2002). When considered substantial, CVR and/or mental health factors were separately added to the main model to assess the contribution of specific factors. Multicollinearity was assessed based on VIF < 10 , tolerance > 0.2 and visual inspection of regression coefficients and 95% CIs (Field, 2013). Also, correlations between GHT duration and cognitive outcome measures, corrected for age and education level, were assessed within the transgender groups.

To secondarily explain cognitive differences between transgender women and cisgender groups, several additional analyses were performed excluding participants with MMSE < 24 or cisgender participants that had previously participated LASA research (to account for practice effects). Lastly, associations of episodic memory with mean estradiol level were assessed for transgender women.

Results

Participant characteristics

Table 1 shows a detailed overview of demographic, cardiovascular, and mental and social information per group. All transgender men had MMSE scores within the normal range, however, more transgender women (5.6%) compared to cisgender women (2.3%) and cisgender men (2.8%) had a deviant score on the MMSE. Transgender men received GHT on average for 30 years, and transgender women for 24 years. Almost all transgender women and men underwent gonadectomy. Three cisgender women and one cisgender man used HRT. Fewer transgender women had hypertension and/or used

Table 1. Descriptive statistics separately per group.

	Cisgender women	Transgender women	Cisgender men	Cisgender women	Transgender men	Cisgender men
N	218	72	218	117	39	117
Age (SD)	66.3 (6.1)	66.0 (6.3)	66.7 (5.9)	63.6 (4.6)	62.3 (5.4)	63.8 (4.6)
Age range	58–87	57–84	57–87	58–80	56–79	57–81
Education (IQR)	5 (3)	6 (4)	5 (3)	7 (2)	7 (4)	7 (2)
Education range	1–9	1–9	2–9	1–9	1–9	2–9
GHT duration in years (SD)	–	24 (9.4)	–	–	30 (8.8)	–
GHT duration range	–	10–45	–	–	10–47	–
17 β -estradiol in pmol/l (IQR) ^a	–	214 (136)	–	–	–	–
17 β -estradiol range	–	102–828	–	–	–	–
% HRT	1.4	–	0.5	1.7	–	0.9
% Gonadectomy	–	94.4	–	–	100 ^M	–
Cognitive functioning						
% MMSE <24	2.3	5.6	2.8	1.7	0	1.7
% Memory problems ^b	37.3	31.9	31.2	37.6	35.9	24.8
CVR factors						
% CVD	18.8	25.0	33.0	16.2	20.5	27.4
% DM	6.9	11.1	13.8	6.0	10.3	7.7
BMI (SD)	27.1 (5.4)	27.6 (6.1)	27.1 (4.0)	26.5 (5.6)	24.7 (3.7)	26.9 (4.1)
% Hypertension ^c	50.9	36.1	62.2	41.4	48.7	52.1
% Smoking	11.5	22.2	11.0	12.0	33.3	12.8
Alcohol consumption:						
- % No	18.3	20.8	8.7	15.4	23.1	11.1
- % Light	52.3	65.3	35.8	52.1	53.8	35.0
- % Moderate	26.6	11.1	41.7	29.1	15.4	45.3
- % Excessive	2.8	2.8	11.5	3.4	7.7	7.7
- % Very excessive	0	0	1.8	0	0	0.9
Mental health						
Anxiety symptoms (IQR)	3 (3)	4 (5)	2 (4)	3 (3)	3 (3)	1 (3)
Depressive symptoms (IQR)	7 (8)	13 (12)	4 (8)	7 (11)	8 (14)	3 (6)
Loneliness (IQR)	0 (2)	4 (7)	1 (2)	0 (1)	2 (4)	0 (2)
% Mental health care ^d	3.7	15.3	3.7	4.3	20.5	4.3

Cisgender group data are presented separately for comparison with transgender women and men, as a subset of cisgender participants was used to match and compare with the smaller number of transgender men;

Continuous data are presented as mean (SD) or as median (interquartile range; IQR);

Education level consists of 9 categories: 1) no completed education, 2) elementary school, 3) lower vocational, 4) general intermediate, 5) intermediate vocational, 6) general secondary school, 7) higher vocational, 8) college, and 9) university;

^MData missing for 1 person.

^aOnly reported for transgender women to secondarily explain cognitive differences.

^bSubjective experience of memory problems (yes/no).

^cHypertension and/or antihypertensive use.

^dPsychological/psychiatric help/hospitalization in the past 6 months.

Abbreviations: BMI: body mass index; CVR: cardiovascular risk; CVD: (current or history of) cardiovascular disease; DM: diabetes mellitus; GHT: gender-affirming hormone therapy; HRT: Hormone-replacement therapy; MMSE: Mini-Mental State Examination.

antihypertensive medication compared to cisgender women and men (Table 1). Regarding lifestyle factors, more transgender women and men smoked and alcohol consumption was overall lower compared to cisgender women and men (Table 1). Transgender women and men had more anxiety symptoms, depressive symptoms, were more lonely, and more received recent mental health care compared to cisgender women and men. For transgender men, differences were most prominent compared to cisgender men (Table 1).

Cognitive functioning differences

Mean test scores per group are shown in Table 2, and group differences (calculated into mean

z-scores) per cognitive domain are shown in Table 3—models A and Figure 1 (black). Overall, the cognitive functioning profile of transgender women was lower compared to cisgender groups. Compared to cisgender women and men, respectively, transgender women scored significantly lower on information processing speed ($b = -0.62$, 95% confidence interval (CI) -0.90 to -0.35 and $b = -0.33$, CI -0.60 to -0.05), episodic memory ($b = -1.28$, CI -1.53 to -1.04 and $b = -0.77$, CI -1.01 to -0.52), and crystallized intelligence ($b = -0.42$, CI -0.75 to -0.10 and $b = -0.41$, CI -0.75 to -0.08). No significant differences were found for executive functioning.

Overall, transgender men had similar cognitive functioning profiles compared to both cisgender

Table 2. Raw cognitive functioning test scores separately per group.

	<i>Cisgender women</i>	<i>Transgender women</i>	<i>Cisgender men</i>	<i>Cisgender women</i>	<i>Transgender men</i>	<i>Cisgender men</i>
Coding task	31.4 (6.6)	27.3 (7.0)	29.3 (6.2)	32.2 (5.7)	32.2 (5.2)	30.6 (5.8)
Range	11–48	11–39	14–45	19–48	20–40	14–45
15WT immediate	26.3 (5.7)	19.3 (5.2)	23.3 (5.8)	27.1 (5.7)	25.2 (6.0)	24.6 (5.3)
Range	12–41	9–32	7–35	13–41	10–35	9–35
15WT delayed	8.8 (2.9)	5.0 (2.6)	7.5 (3.1)	9.3 (2.8)	7.9 (3.3)	8.2 (2.9)
Range	1–15	0–11	0–14	3–15	0–15	0–13
Fluency D	13.1 (4.8)	11.8 (5.7)	13.0 (5.1)	14.0 (5.2)	13.2 (4.7)	13.9 (5.0)
Range	3–35	2–30	1–28	3–35	6–23	4–28
Fluency animals	22.3 (6.0)	21.1 (6.9)	21.8 (6.2)	23.7 (6.3)	24.7 (6.5)	23.5 (6.1)
Range	1–40	8–37	2–40	1–40	11–42	7–40
Digit span forward	8.3 (1.9)	8.4 (2.3)	8.5 (2.1)	8.6 (1.9)	9.2 (2.2)	8.7 (2.2)
Range	4–14	4–16	2–16	5–14	5–14	2–16
Digit span backward	6.1 (1.8)	5.8 (2.3)	5.9 (2.1)	6.3 (1.8)	6.5 (2.0)	6.2 (2.2)
Range	2–11	2–11	2–12	3–11	4–12	2–12
Vocabulary test	13.9 (3.6)	13.0 (5.1)	13.8 (3.4)	14.3 (3.5)	14.5 (4.1)	14.0 (3.3)
Range	0–20	1–20	1–19	2–20	1–20	1–19

Cisgender group data are presented separately for comparison with transgender women and men, as a subset of cisgender participants was used to match and compare with the smaller number of transgender men;

Data are presented as mean (SD);

Abbreviations: 15WT: 15-Word Test (immediate or delayed recall).

Table 3. Linear regression analyses comparing cognitive functioning between groups (models a), separately per group comparison and cognitive domain, including models (B–D) secondarily adjusting for cardiovascular and mental health factors.

	1. <i>Transgender women vs. cisgender women</i>			2. <i>Transgender women vs. cisgender men</i>		
	<i>B</i>	<i>95% CI</i>	<i>ΔB (%)</i>	<i>B</i>	<i>95% CI</i>	<i>ΔB (%)</i>
Information processing speed						
Model A: Group	−0.62	−0.90 to −0.35		−0.33	−0.60 to −0.05	
Model B: + CVR	−0.56	−0.83 to −0.29	10	−0.32	−0.61 to −0.02	3
Model C: + Mental health	−0.30	−0.59 to −0.01	52	−0.01	−0.34 to 0.31	96
Model D: + All factors	−0.34	−0.63 to −0.04	46	−0.08	−0.41 to 0.25	76
Episodic memory						
Model A: Group	−1.28	−1.53 to −1.04		−0.77	−1.01 to −0.52	
Model B: + CVR	−1.24	−1.50 to −0.99	3	−0.75	−1.01 to −0.49	2
Model C: + Mental health	−1.12	−1.39 to −0.85	13	−0.60	−0.88 to −0.31	29
Model D: + All factors	−1.14	−1.42 to −0.86	11	−0.64	−0.94 to −0.35	16
Executive functioning						
Model A: Group	−0.13	−0.33 to 0.06		−0.11	−0.32 to 0.10	
Model B: + CVR	−0.07	−0.27 to 0.12	46	−0.02	−0.24 to 0.21	85
Model C: + Mental health	0.07	−0.15 to 0.28	150	0.17	−0.07 to 0.42	256
Model D: + All factors	0.08	−0.13 to 0.29	162	0.21	−0.05 to 0.46	283
Crystallized intelligence^a						
Model A: Group	−0.42	−0.75 to −0.10		−0.41	−0.75 to −0.08	
Model B: + CVR	−0.46	−0.80 to −0.12	9	−0.28	−0.66 to 0.10	31
Model C: + Mental health	−0.11	−0.46 to 0.25	75	0.14	−0.25 to 0.53	134
Model D: + All factors	−0.18	−0.55 to 0.19	57	0.20	−0.22 to 0.62	149
3. <i>Transgender men vs. cisgender women</i>						
Information processing speed						
Model A: Group	−0.01	−0.37 to 0.35		0.27	−0.09 to 0.62	
Model B: + CVR	−0.07	−0.45 to 0.31	690	0.20	−0.20 to 0.60	24
Model C: + Mental health	0.05	−0.32 to 0.43	677	0.34	−0.04 to 0.72	27
Model D: + All factors	−0.05	−0.46 to 0.35	485	0.25	−0.17 to 0.67	5
Episodic memory						
Model A: Group	−0.43	−0.79 to −0.08		−0.01	−0.36 to 0.35	
Model B: + CVR	−0.39	−0.78 to −0.01	9	−0.01	−0.40 to 0.37	188
Model C: + Mental health	−0.38	−0.75 to −0.01	12	0.15	−0.23 to 0.53	3065
Model D: + All factors	−0.36	−0.76 to 0.04	16	0.10	−0.30 to 0.50	2083
Executive functioning						
Model A: Group	0.11	−0.14 to 0.35		0.10	−0.17 to 0.38	
Model B: + CVR	0.11	−0.15 to 0.37	4	0.13	−0.17 to 0.44	31
Model C: + Mental health	0.11	−0.15 to 0.37	3	0.16	−0.14 to 0.45	54
Model D: + All factors	0.08	−0.20 to 0.37	22	0.13	−0.20 to 0.46	27
Crystallized intelligence						
Model A: Group	−0.08	−0.45 to 0.29		0.13	−0.26 to 0.51	
Model B: + CVR	−0.03	−0.43 to 0.38	65	0.10	−0.31 to 0.51	23
Model C: + Mental health	−0.07	−0.46 to 0.32	11	0.21	−0.19 to 0.62	67
Model D: + All factors	−0.07	−0.50 to 0.35	8	0.16	−0.25 to 0.58	29
4. <i>Transgender men vs. cisgender men</i>						

Models A=mean z-score differences between the transgender and cisgender groups, separately per Group comparison (1–4) and cognitive domain;

Models B, C and D=mean z-score differences between the transgender and cisgender groups after correcting for B) cardiovascular risk (CVR) factors, C) mental health factors, and D) all factors combined;

B = regression coefficient of the Group dummy;

ΔB (%) = percentage change of *B* after correcting for additional factors in models B–D;

^aComparison 1: *N*=217, 2: *N*=211, 3: *N*=140, 4: *N*=134;

Bold=significance based on 95% CI for models A and *ΔB*>10% and relevant (>0.1 z-score) for models B–D.

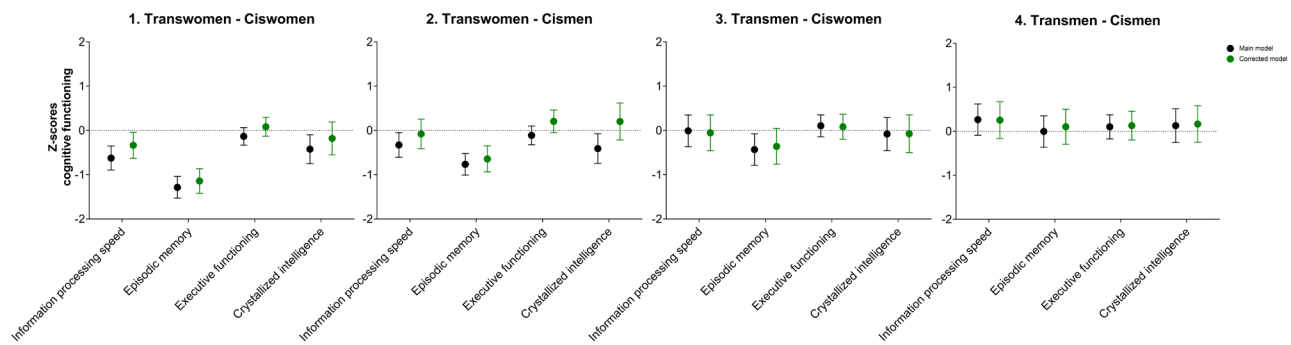


Figure 1. Differences in cognitive functioning between trans- and cisgender groups per cognitive domain with (green) and without (black) correction for cardiovascular and mental health factors. Data are displayed per group comparison (1–4) as z-scores with zero as the mean of the cisgender reference groups (displayed as dotted lines) and with dots (and 95% confidence intervals) as the mean difference of the transgender groups vs. the cisgender groups. Therefore, overlap with the zero-line means no significant group difference. Black dots represent the main regression model (model A) with cognitive functioning domains as dependent variables and Group (1–4) as independent variables. Green dots represent the corrected model (model D) with cognitive functioning domains as dependent variables and Group (1–4), cardiovascular and mental health factors as independent variables.

groups. Only on the domain of episodic memory they scored lower compared to cisgender women, $b = -0.43$, CI -0.79 to -0.08 , but similar to cisgender men. Results per test within cognitive domains were similar to the average domain results.

Transgender women and men, respectively, reported memory problems equal to cisgender women (*Table 1*; $b=0.79$, CI 0.45 to 1.39 ; $b=0.93$, CI 0.44 to 1.97) and men ($b=1.04$, CI 0.58 to 1.84 ; $b=1.70$, CI 0.78 to 3.70). GHT duration was not significantly associated with any cognitive outcome measure within the transgender groups.

Role of cardiovascular and mental health factors

The corrected models are shown in *Table 3*—models B–D and *Figure 1* (model D in green). For all cognitive domains, the addition of all CVR and mental health factors (models 1–2D) resulted in substantially less negative regression coefficients of the difference between transgender women and both cisgender groups. This was largely the result of adjusting for mental health factors (models 1–2C), specifically loneliness, anxiety, and depressive symptoms, which overall attenuated cognitive differences between these groups. CVR factors also slightly attenuated the difference between transgender women and cisgender men on crystallized intelligence (models 1–2B). This could not be explained by any of the CVR factors individually. For episodic memory,

large differences between transgender women and cisgender groups remained after adjustment.

Overall, the addition of any clustered factors did not lead to substantial changes in the differences between transgender men and cisgender women (models 3B–D) and did therefore not substantially explain the difference between these groups on episodic memory. The regression coefficient of the (non-significant) difference on episodic memory between transgender men and cisgender men substantially changed in favor of transgender men due to adjusting for mental health factors (models 4B–D), particularly depressive symptoms. No clusters of factors led to substantial changes between these groups on information processing speed, executive functioning, or crystallized intelligence.

Subgroup analyses

To explain the large (remaining) differences on episodic memory between transgender women and cisgender groups, several additional analyses were performed. First, since more transgender women had a deviant score on the MMSE compared to both cisgender groups, subgroup analyses including only participants with MMSE scores in the normal range were conducted. Results, corrected for age and education level, were similar to the main analyses: $N=280$, $b=-1.31$, CI -1.55 to -1.08 compared to cisgender women and $N=278$, $b = -0.79$, CI -1.03 to -0.55 compared to cisgender men.

Second, to account for possible practice effects of cisgender participants of earlier cohorts, subgroup analyses were conducted comparing transgender women to the most recent cisgender cohort, corrected for age and education level. Similar results were found: cisgender women, $N=223$, $b=-1.38$, CI -1.64 to -1.12 ; cisgender men, $N=215$, $b=-0.84$, CI -1.10 to -0.59 .

Last, linear regression analyses were conducted to assess associations of episodic memory and sex-hormone exposure in transgender women. No significant association with mean estradiol level (in pmol/l) was found, $N=65$, $b=0.03$, CI -0.10 to 0.15 (reported per 100 units). Nor with GHT duration in years, $N=72$, $b=0.01$, CI -0.01 to 0.03 .

Discussion

This study assessed cognitive functioning differences between older transgender women and men receiving long-term GHT and age-matched cisgender women and men. Overall, transgender women had significantly and substantially lower cognitive functioning profiles compared to both cisgender groups, which was most prominent for episodic memory. Subgroup analyses excluding participants with deviant MMSE scores, which applied to more transgender women, showed similar episodic memory differences. These findings are not in line with our expectations based on only subtle differences between these groups in a previous study (van Heesewijk et al., 2021) and previous literature suggesting neuroprotective effects of sex-hormones, particularly estrogens (Collins et al., 2009; Jenkins et al., 2004; Lee et al., 2016; Shilling et al., 2003; Woolie et al., 2015; Zwart et al., 2015). However, a recent study by Hughto et al. (2023) showed more dementia diagnoses in older (65+) transgender women compared to cisgender women and men. Although dementia and lower cognitive functioning are not comparable, the group differences are in line with the current study. Transgender men had similar cognitive functioning profiles compared to both cisgender groups. This was partly in line with the results of Hughto and colleagues, which showed more dementia compared to only cisgender women.

Furthermore, to explain these cognitive differences (and similarities) between trans- and cisgender groups, we took into account the differences in CVR and mental health factors between these groups. Differences in mental health factors, specifically loneliness, anxiety, and depressive symptoms, largely or fully explained the differences (statistically significant or not) between transgender women and cisgender groups on information processing speed, executive functioning, and crystallized intelligence. CVR factors overall explained part of the difference with cisgender men on crystallized intelligence. Differences on episodic memory could only partly be explained by mental health differences. For transgender men, accounting for mental health factors, specifically depressive symptoms, only changed the difference with cisgender men on episodic memory in favor of transgender men. Since transgender groups showed more mental health challenges than cisgender groups, these findings are in line with previous research showing negative associations between mental health problems and cognitive functioning (Brailean et al., 2017; Knight & Baune, 2018), suggesting that mental health challenges are a risk factor for lower cognitive functioning.

Taking these findings together, we found few and slight differences in cognitive functioning between cisgender groups and transgender men but multiple and larger differences with transgender women. This could largely be explained by more mental health challenges among transgender groups. However, the marked difference on episodic memory between transgender women and cisgender groups could not be (fully) explained.

Episodic memory

Episodic memory refers to the ability to recall life events and it predominantly involves the hippocampus and medial temporal lobe, which retrieve, encode, and combine this information from various brain areas (Dickerson & Eichenbaum, 2010). This cognitive domain can be assessed in different ways such as verbally and spatially and is associated with sex: women generally perform better than men on verbal episodic memory tasks

(as used in the current study) and men typically outperform women on visuospatial episodic memory tasks (Asperholm et al., 2019; Herlitz & Rehnman, 2008; Rey, 1964). These sex differences might be a result of multiple factors including biological factors such as sex hormones and environmental factors such as (gendered) socialization and education (Asperholm et al., 2019; Herlitz & Rehnman, 2008). Although the current study did not show associations of GHT duration with cognitive functioning, the potential influence of sex hormones is supported by previous studies in transgender individuals starting GHT showing changes in the direction of the group with which they share their gender identity on sex-biased cognitive tasks such as verbal memory and fluency, and visuospatial ability (Gooren & Giltay, 2014; Karalexi et al., 2020; Nguyen et al., 2018). This could explain the slightly lower performance of transgender men on episodic memory compared to cisgender women, but not the lower performance of transgender women compared to both cisgender women *and* men. Here, we discuss possible methodological and neurobiological explanations for the latter finding.

First, the possible explanation of practice effects among cisgender participants was explored since LASA Wave I consists of three cohorts, of which two included participants who had previously participated in LASA research. We conducted subgroup analyses with the newest cohort only, which showed similar results. Since protocols for trans- and cisgender participants were otherwise identical, methodological explanations for the difference in episodic memory between transgender women and cisgender groups seem unlikely.

Second, several sex-hormone related mechanisms could be potential explanations for this difference such as the timing of initiation and/or duration of estrogen exposure. There was a distinct difference in estradiol exposure between transgender women and the cisgender groups: Transgender women in this study all received GHT and cisgender women were postmenopausal (as inferred by their age); therefore, levels approximating zero can be expected (Decaroli & Rochira, 2017; Roeca et al., 2000). Could this suggest that estradiol exposure in older age is less beneficial

for cognitive functioning/episodic memory? In the current study, no association of cognitive functioning with mean estradiol level over the years (nor with GHT duration) in transgender women was found. Additionally, in general, research in (postmenopausal) cisgender women shows neuroprotective effects of estradiol which might only be true when HRT is started early in menopause, whereas later start may increase the risk of cognitive decline or even dementia (Luine, 2014). This might be due to downregulation of estrogen receptors (ERs) in the brain following a period of sex-hormone deprivation limiting estradiol's neuroprotective potential.²

The observed effects could also be due to androgen deprivation: A similar mechanism of downregulation of ER expression might apply to transgender women who have been exposed to high levels of testosterone prior to the start of GHT, such as for transgender women in the current study. Animal studies show beneficial effects of estradiol in female but not in male hippocampi as a result of downregulation of ERs after a prenatal (and/or pubertal Kight and McCarthy (2020)) testosterone surge in male rats rodents (Gillies & McArthur, 2010). This may suggest that in transgender women, estrogen's neuroprotective ability might be (partly) lost as a result of testosterone exposure prior to GHT.

Other potential sex-hormone mediated mechanisms include continuous exposure to estradiol and the lack of progesterone supplementation in GHT for transgender women. Studies in rats suggest that (long-term) continuous, as opposed to cyclic, estradiol exposure might negatively impact cognitive functioning by downregulating ERs in multiple brain areas after oophorectomy (Brown et al., 1996; Sherwin & Henry, 2008). Progesterone's role in cognitive functioning is not yet well understood due to low-quality evidence. However, research in pregnant, postmenopausal, and naturally cycling cisgender women does not show clinically relevant or consistent associations (Henderson, 2018).

Mental health

The higher prevalence of mental (and social) health challenges in transgender individuals

played an important role in cognitive differences, particularly between transgender women and cisgender women and men. The minority stress theory might (partly) explain these challenges. Transgender individuals may experience minority stress resulting from stigma in the form of internal and external stressors related to a transgender identity (Pellicane & Ciesla, 2022). Particularly transgender women are disproportionately subject to external stressors such as discrimination and violence (Glick et al., 2018). The minority stress theory poses that this may lead to more mental health challenges, as was confirmed in older transgender individuals by Fredriksen-Goldsen et al. (2014), identifying victimization and internalized stigma as the most important mediators of gender identity on mental and physical health outcomes. However, studies in this population are limited. Importantly, stress may also influence cognitive functioning by dysregulating the hypothalamic-pituitary-adrenal axis, directly influencing brain regions such as the hippocampus (Ali et al., 2018; McEwen et al., 2015). This warrants research on transgender individual's experiences and other determinants of mental health.

Clinical relevance

To put the differences in cognitive functioning between transgender women and cisgender groups into perspective, we here discuss subjective report of memory problems, and compare the results of this study to the literature and available norm scores. In our study, transgender women, having lower episodic memory scores, subjectively reported memory problems equal to those of cisgender groups. Thus, they did not appear to experience more hindrance than the cisgender groups. However, these results are not in line with recent studies in the U.S. showing that more older (45+) transgender individuals and SGM individuals reported increased confusion or memory loss in the past year compared to cisgender and non-SGM individuals, respectively (Cicero et al., 2023; Flatt et al., 2021). Differences might be explained by differences in the question asked or by cultural differences in interpreting and/or answering the question. Also, memory complaints

are not always associated with impaired cognitive functioning (Purser et al., 2006). Furthermore, the current study showed more and larger differences, especially on episodic memory, between transgender women and cisgender groups than the previous study by van Heesewijk et al. (2021) with a smaller and younger sample of only transgender women ($N=37$, mean age 62.3y) and cisgender groups using different protocols. To explain the clinical relevance of these differences, we compared the mean raw scores of transgender women, and cisgender men and women of both studies (available upon request) to norm scores (de Vent et al. 2016; www.andi.nl). All groups in both studies scored within the normal range (<1.5 z-score difference) and the size of the episodic memory differences between the studies could be explained by relative differences between the cisgender cohorts. Of note, transgender women did consistently score lower than average in both studies on most cognitive domains.

Strengths and limitations

This study contributes to our understanding of the understudied field of health outcomes in older transgender women *and* men due to its extensive assessment of cognitive functioning, a critical health aspect among the growing older (transgender) population. Identical data for all groups were collected using the well-established LASA protocol also providing a large cisgender control sample. Moreover, we examined to what extent differences in CVR and mental health factors could account for group differences in cognitive functioning.

Limitations of this study include the absence of longitudinal data, potential influence of the Covid-19 pandemic and lack of consistent/recent blood tests. First, the cross-sectional data limit causal inference, because the temporality behind the associations between CVR and mental health factors on the one hand and cognitive functioning on the other remains unclear. We expect that CVR and mental health factors largely mediate the differences between the trans- and cisgender groups on cognitive functioning, but reverse causality may also play a role, with cognitive functioning affecting CVR and mental health factors.

Second, data of transgender participants were collected in the summer of 2021 during the Covid-19 pandemic, when there were some safety measures in place in the Netherlands, whereas cisgender data were collected pre-pandemic. Symptoms of anxiety, depression, and loneliness might have been more prevalent during the pandemic than before (Holwerda et al., 2023). Nevertheless, the impact of the pandemic on the results may have been minor, as cognitive test scores of transgender women in the current study were similar to those of a previous study conducted between 2008 and 2012 (van Heesewijk et al., 2021), and participants themselves reported a limited impact of the pandemic on their mental health.

Last, estradiol levels were secondarily collected from ACOG to explain the episodic memory results in transgender women. Therefore, no recent levels were available, and average values per person over the years comprised 2 to 16 values per transgender woman from 2004 until 2018. Furthermore, no estradiol levels of cisgender participants were collected.

Suggestions for future research

We recommend longitudinal studies with larger sample sizes allowing for subgroup analyses with more variation in age (including 70+) and hormone use such as no GHT, half-dose and recent start of GHT. Also studies assessing sex-hormone receptor expression particularly in the hippocampus, are important to explore potential sex-hormone mediated mechanisms involved in the cognitive functioning of transgender women particularly. Last, research on mental health challenges and its determinants in the (older) transgender population is warranted.

Conclusions

In light of the general lack of information and clinical guidelines regarding health outcomes in older transgender individuals, this study provides valuable information on cognitive functioning and potential risk factors among older long-term GHT receiving transgender women and men. Transgender women had significantly and substantially lower cognitive functioning

compared to cisgender groups, which was largely explained by a higher prevalence of mental health challenges. Also, for transgender men, mental health challenges partly explained cognitive differences with cisgender men. Importantly, however, the small cognitive differences between transgender men and cisgender groups do not suggest adverse or beneficial long-term testosterone effects on cognitive functioning. These findings warrant further research and clinical awareness of mental and cognitive health and other potential risk factors such as minority stress and sex-hormone exposure, especially in older transgender women.

Notes

- 1) No completed education, 2) elementary school, 3) lower vocational, 4) general intermediate, 5) intermediate vocational, 6) general secondary school, 7) higher vocational, 8) college, and 9) university.
- ERs are found in multiple brain areas among which the hippocampus (important for episodic memory) and can have a dose-dependent influence on memory (Bean et al., 2014). The number of ERs and estradiol's ability to improve cognitive functioning declines with age, which suggests a critical therapeutic window for estradiol's neuroprotective effect.

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Disclosure statement

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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- a. The authors have not entered into an agreement with the funding organization that has limited their ability to complete the research as planned and publish the results.
- b. The authors have had full control of all the primary data.
- c. The authors are willing to allow the journal to review their data if requested.

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Appendix

Table A1. Alcohol consumption index for Longitudinal Aging Study Amsterdam (Hoogendijk et al., 2020; Huisman et al., 2011). This table was adapted from (Garretsen, 1983).

Number of days drinking alcohol	Number of alcohol consumptions each time			
	6 or more	4-5	2-3	0-1
5-7 days per week	Very excessive	Excessive	Moderate	Light
3-4 days per week	Excessive	Moderate	Moderate	Light
1-2 days per week	Excessive	Moderate	Light	Light
1-3 days per month	Moderate	Light	Light	Light
<1 day per month	Light	Light	Light	Light

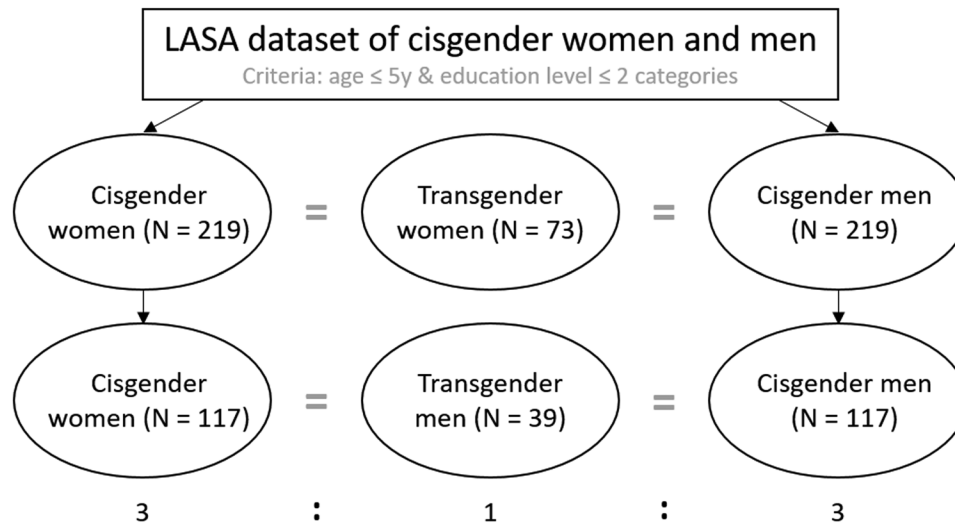


Figure A1. Overview of matching process. Transgender participants were matched 1:3 on age ($\leq 5y$) and education level (≤ 2 categories) to cisgender men and women. Due to the smaller sample of transgender men, a selection of cisgender individuals that were already matched to transgender women, were matched to transgender men.