Gender-affirming hormone treatment and cognitive function in transgender young adults: a systematic review and meta-analysis

Maria A. Karalexia,b, Marios K. Georgakisa, Nikolaos G. Dimitrioua, Theodoros Vichosa, Andreas Katsimprisa, Eleni Th. Petridoua,c, Fotios C. Papadopoulosb,*

a Department of Hygiene, Epidemiology and Medical Statistics, Medical School, National and Kapodistrian University of Athens, Athens, Greece
b Department of Neuroscience, Psychiatry, Uppsala University, Uppsala University Hospital, Uppsala, Sweden
Unit of Clinical Epidemiology, Karolinska Institute, Stockholm, Sweden

A R T I C L E   I N F O
Keywords:
- gender-affirming hormone treatment
- transgender
- gender incongruence
- cognitive function
- visuospatial ability
- meta-analysis

A B S T R A C T
Background: Previous studies have examined whether steroid hormone treatment in transgender individuals may affect cognitive function; yet, their limited power does not allow firm conclusions to be drawn. We leveraged data from to-date literature aiming to explore the effect of gender-affirming hormone administration on cognitive function in transgender individuals.

Methods: A search strategy of MEDLINE was developed (through June 1, 2019) using the key terms transgender, hormone therapy and cognitive function. Eligible were (i) cohort studies examining the longitudinal effect of hormone therapy on cognition, and (ii) cross-sectional studies comparing the cognitive function between treated and non-treated individuals. Standardized mean differences (Hedges' g) were pooled using random-effects models. Study quality was evaluated using the Newcastle-Ottawa Scale.

Outcome: Ten studies (seven cohort and three cross-sectional) were eligible representing 234 birth-assigned males (aM) and 150 birth-assigned females (aF). The synthesis of cohort studies (n = 5) for visuospatial ability following hormone treatment showed a statistically significant enhancement among aF (g = 0.55, 95% confidence intervals [CI]: 0.29, 0.82) and an improvement with a trend towards statistical significance among aM (g = 0.28, 95% CI: -0.01, 0.58). By contrast, no adverse effects of hormone administration were shown. No heterogeneity was evident in most meta-analyses.

Interpretation: Current evidence does not support an adverse impact of hormone therapy on cognitive function, whereas a statistically significant enhancing effect on visuospatial ability was shown in aF. New longitudinal studies with longer follow-up should explore the long-term effects of hormone therapy, especially the effects on younger individuals, where there is greater scarcity of data.

1. INTRODUCTION

Transgender individuals (shortened as trans) experience a discordance between their personal sense of their gender (their gender identity) and the sex assigned to them at birth. Transgender is an umbrella term including not only people whose gender identity differs from their sex assigned at birth (trans men and trans women), but also people who are not exclusively masculine or feminine (non-binary or genderqueer, bigender, pangender, genderfluid or agender) (Drescher et al., 2012; Winter et al., 2016). Natal sex, either male or female, is typically designated according to the appearance of a newborn’s genitalia (Nguyen et al., 2018). For the purposes of the present study, we use the terms natal sex and sex assigned at birth interchangeably to refer to this same concept. In 2013, the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) established the term gender dysphoria (GD), which refers to the discomfort or distress caused in an individual by the incongruence between their gender identity and their birth-assigned sex (Beek et al., 2016; Kraus, 2015). Nonetheless, it should be noted that GD diagnosis has been argued and upcoming efforts propose the removal of gender incongruence from the list of mental and behavioral disorders in DSM in an effort to avert the potential stigma and associated challenges transgender people may face (Reed et al., 2016; Winter et al., 2016). In the latest version of the International Classification of Diseases (ICD-11), the diagnosis of gender incongruence is included in a separate chapter on conditions related to sexual health (Drescher et al., 2012; Reed et al., 2016).
Crude estimates of the prevalence of transgender people rely on indirect methods and they are gauged by the number of individuals pursuing hormonal treatment or other surgical options. The reported overall incidence of transgender people is estimated to 4.6 per 100,000 individuals; 2.6 for trans men and 6.8 for trans women (Arcelus et al., 2015; Collin et al., 2016). There is an upward trend in the incidence of transgender people mainly due to the increased number of transgender individuals, who pursue gender-affirming health care over the past decade (Dhejne et al., 2014; Wiepjes et al., 2018). Concurrently, there has been a dramatic increase in younger transgender individuals seeking medical care over the last years, among whom birth-assigned females (aF) are overrepresented (Littman, 2018; Skordis et., 2018). Gender-affirming health care in young adolescents going through puberty usually involves the administration of hormonal puberty blocking agents, namely gonadotropin-releasing hormone analogues. Older adolescents and adults typically seek masculinizing or feminizing steroid hormones, gender reassignment surgery or several other healthcare services (Winter et al., 2016). Assigned female transgender people typically take testosterone, while assigned males (aM) typically take estradiol with or without androgen blockers (Drescher et al., 2012; Nguyen et al., 2018).

The increased administration of gender-affirming hormone therapy in transgender individuals has raised concerns about potential adverse health effects of the treatment (Mehringer and Dowshen, 2019; Shadid et al., 2019). Several studies have focused on the potential impact of gender-affirming therapy on cognitive function given the accumulating and long debated evidence concerning gender differences in cognition (Nguyen et al., 2018; Nota et al., 2017). Previous research has shown that aF perform better than aM on verbal tests, perceptual speed, memory for object location and fine motor skills, while aM outperform aF on certain mathematical tasks, such as approximate arithmetic, visuospatial ability, targeted motor skills and map reading (Slabbekoorn et al., 1999; Van Goosen et al., 1994). Current evidence supports that gender differences in math performance are small, particularly in de-.

2. Methods

The present systematic review and meta-analysis was conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000) (Supplementary Table 1) based on a predefined protocol.

2.1. Search strategy and eligibility criteria

Two independent reviewers (T.V., N.D.) performed an in-depth search of the Medline database from its inception up to June 1, 2019 using combinations of the following MeSH terms: “transgender”, “gender dysphoria”, “hormone therapy” and “cognitive function”; the complete search strategy is available in the Supplementary Methods. We set no limitations on language and publication year. Articles were initially selected based on title and abstract; the full-texts were thereafter obtained and reviewed. Pairs of reviewers performed the selection of studies independently and blindly to each other. Reference lists of the eligible studies and identified relevant reviews were subsequently hand searched for potentially additional eligible studies (“snowball procedure”). Eligible studies were evaluated for overlap by contacting the authors (Van Goosen et al., 1994, 1995; Van Goosen et al., 2002). We contacted the corresponding authors of eligible studies in case of missing data in the published articles, inquiries regarding the eligibility of the study or ambiguous cases of potential population overlap between studies.

Eligible studies included cohort and cross-sectional studies that assessed the relationship between gender-affirming hormone therapy and cognitive function in transgender individuals. Acknowledging the controversies in the diagnosis of GD, we primarily searched for studies on transgender individuals who explicitly met the diagnostic criteria of a GD diagnosis. The most comprehensive definition of GD was selected, preferably the assessment of GD by psychiatrists based on the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM IV). However, to avoid publication bias studies using alternative diagnostic criteria or not specifying the diagnostic method, as well as studies on transgender people not clearly meeting the criteria of GD were also considered eligible. To this end, we avoided the term GD for the purposes of the present study to prevent a potential misclassification bias, but we used only the term transgender individuals who received gender-affirming hormone treatment irrespectively of meeting or not the criteria of a GD diagnosis. We included cohort studies assessing any cognitive domain among aF or aM transgender individuals in at least two different serial assessments (pre- and post-treatment), as well as cross-sectional studies comparing aF or aM transgender individuals who were under gender-affirming treatment versus those who did not receive any treatment. The measurement of cognitive function was estimated using validated standardized tests, which examined one or more domains of cognition.

2.2. Data extraction and quality assessment

General information (year, author, journal, region of origin and study period), study characteristics (design, duration of follow-up, description of participants), cohort size, mean age, age range, as well as characteristics of the hormonal treatment (type of intervention, onset of treatment, average dosage, average period exposed to treatment, administration route) were abstracted in a pre-piloted spreadsheet. Furthermore, the different cognitive tests were abstracted and categorized based on the properties of the test in the main cognitive domains, namely attention, computation, motor coordination, verbal memory, verbal reasoning, verbal working memory, visual working memory, total working memory and visuospatial ability. The final classification of the tests by cognitive domain, reviewed by two clinical neuropsychologists (T.H. and J.I.) and a senior psychiatrist (F.P.) is available in Supplementary Table 2. Regarding the results of the studies, we extracted the mean values and standard deviations of scores achieved at each test before and after the intervention for cohort studies, as well as the scores achieved by treated and non-treated individuals in cross-sectional studies.

Two independent reviewers conducted the data abstraction and quality assessment of the eligible studies (N.D., I.S.). The quality of each study was evaluated using the Newcastle-Ottawa Quality Assessment
Scale (NOS) (Wells et al., 2011). In the ‘Selection’ section of the NOS scale, studies including individuals diagnosed with GD according to DSM-IV and seeking a gender-affirming hormone treatment would be considered truly representative of the exposed cohort/sample, whereas studies on transgender people not clearly meeting the criteria of GD were also considered representative of the community and were allotted a star. Furthermore, the “Selection of the non-exposed cohort” category was not evaluated given that the eligible cohort studies performed a comparison between pre- and post-treatment of each study participant (absence of non-exposed group); for the same reason all formed a comparison between pre- and post-treatment of each study category was not evaluated given that the eligible cohort studies per-
formance via a validated cognitive test were allotted a star. Ad-
deelotted a star. Furthermore, the studies on transgender people not clearly meeting the criteria of GD DSM-IV and seeking a gender a

3.2. Characteristics of included studies

The descriptive characteristics of the eligible studies are summarized in Table 1. Briefly, eight studies were conducted in Europe (Burke et al., 2016a; Gomez-Gil et al., 2009; Miles et al., 2006; Miles et al., 1998; Schoning et al., 2010; Slabbekoorn et al., 1999; Van Goozen et al., 1994; Van Goozen et al., 2002), one in the USA (Friedman, 2000) and one in both Europe and the USA (Haraldsen et al., 2005). Six studies were cohort (Burke et al., 2016a; Haraldsen et al., 2005; Miles et al., 2006; Slabbekoorn et al., 1999; Van Goozen et al., 1994; Van Goozen et al., 2002) and three cross-sectional (Friedman, 2000; Miles et al., 1998; Schoning et al., 2010), whereas one study presented both a longitudinal and a cross-sectional analysis (Gomez-Gil et al., 2009). Overall, there were 91 aM and 131 aF transgender individuals in the cohort studies and 143 aM and 19 aF transgender individuals in cross-sectional studies. The gender-affirming hormone treatment mainly consisted of androgen for aF individuals and estrogen usually combined with antiandrogen for aM; however, the dosages and frequencies of hormonal administration showed a large variability among the eligible studies. In addition, the majority of eligible studies lacked information on history of treatment prior to the gender-affirming hormone protocol including the type, dosage and frequency of medications administered. Though variable across studies, the mean age at first cognitive assess-
ment was 36.0 years for aM and 25.6 years for aF individuals. For co-
hort studies, the follow-up period ranged between 2 and 12 months. The specific cognitive tests are described in detail in Supplementary Table 2. In brief, visuospatial ability (6 cohort and 2 cross-sectional studies) and verbal memory (5 cohort and 3 cross-sectional studies) were the most commonly assessed cognitive domains across studies, followed by visual memory (5 cohort and 1 cross-sectional studies) and verbal reasoning (4 cohort and 2 cross-sectional studies).

3.3. Quality of studies

High quality was recorded for the majority of the included studies with only two cross-sectional studies losing over two NOS points due to short follow-up (<6 months), inadequate follow-up (<80%) and non-comparability on other risk factors. However, all studies ascertained the exposures and outcomes of interest using validated measures, whereas the follow-up was adequate (>80%) in all cohort studies (Supplementary Table 4).

3.4. Synthesis of results

The pooled analysis of cohort studies showed a significant medium-sized enhancement in visuospatial ability following gender-affirming hormone treatment for 3-12 months in aF transgender (N = 117) indi-
viduals (g = 0.55, 95% CI: 0.29, 0.82; n = 5 study arms (Burke et al.,
2016a; Haraldsen et al., 2005; Slabbekoorn et al., 1999; Van Goozen
et al., 1994; Van Goozen et al., 2002); Fig. 2) without significant be-
tween-study heterogeneity (I² = 0.0%, p for heterogeneity = 0.856). No statistically significant changes were found in the remaining cogni-
tive domains (verbal memory, verbal reasoning, verbal working
memory, computation, motor coordination) between pre-treatment and post-treatment performance (Fig. 2); of note, the pooled analysis in aF individuals was not feasible for cross-sectional studies due to insuffi-
cient data.

Pooling data from cohort studies on aM transgender individuals (N = 91) showed an enhancement, albeit with a trend towards statistical significance, in visuospatial ability following gender-affirming hormone treatment (g = 0.28, 95% CI: -0.01, 0.58; n = 5 study arms (Haraldsen et al.,
2005; Miles et al., 2006; Slabbekoorn et al., 1999; Van Goozen
et al., 2002); I² = 0.0%, p for heterogeneity = 0.561; Fig. 3). The pooled analysis of cross-sectional studies showed higher performance in verbal working memory among gender-affirming hormone treated (N = 50) compared to non-treated (N = 61) aM individuals (g = 0.52,
95% CI: 0.13, 0.90; n = 2 study arms (Friedman, 2000; Miles et al., 1998); $I^2 = 0.0\%$, $p$ for heterogeneity = 0.671; Supplementary Fig. 1). Meta-regression analyses did not show any significant modifying effect of the major confounding factors, namely publication year, average follow-up period, country of origin and mean age, on the observed associations ($p = 0.225-0.972$; Supplementary Table 5).

4. Discussion

4.1. Principal findings

This comprehensive systematic review and meta-analysis summarizes evidence from 10 studies that examined the relationship between gender-affirming steroid hormonal therapy and cognitive function in trans gender young adults. All but one studies focused on young adults (age range 16.0-42.0 years) examining the effect of post-pubertal gender-affirming hormonal treatment on different cognitive domains. Identified studies used mainly longitudinal, but also cross-sectional design and focused mostly on visuospatial ability and verbal memory. The results showed a statistically significant enhancement in visuospatial ability in aF following gender-affirming hormone treatment. The pooling of cross-sectional studies showed an improved performance in verbal working memory among treated compared to non-treated aM individuals. Importantly, the synthesis of to-date published literature did not support an adverse effect of gender-affirming hormone administration on any cognitive domain. Despite the variability in exposure and outcome assessment, no between-study heterogeneity was evident in most meta-analyses; in addition, meta-regression analyses showed no significant effect of potential confounders on the associations of interest.

4.2. Previous literature-Interpretation of results

A persistent finding among studies of gender differentials in cognitive performance is that aM seem to outperform aF on tests of visuospatial skills, whereas aF surpass aM on tests of verbal abilities (Breda and Napp, 2019; Kimura, 1996; Maccoby and Jacklin, 1974; Palmiero et al., 2016; Wei et al., 2016); these differences seem to be mainly attributed to circulating hormonal changes (Ali et al., 2018; Beking et al., 2018; Burke et al., 2016b; Nguyen, 2018; Silverman et al., 1999). Consistently with the results of these studies, the present meta-analysis suggests that an androgenic hormonal environment may have a beneficial effect on visuospatial ability. Similar results were found in studies on aF with congenital adrenal hyperplasia showing enhanced spatial ability (Berenbaum, 2001), as well as in studies supporting that human spatial ability may be beneficially affected by prenatal androgens (Beking et al., 2018; Nguyen et al., 2017). In particular, second trimester testosterone levels seem to predict spatial ability positively in aF and negatively in aM at age seven (Grimshaw et al., 1995). Moreover, according to a twin study, aF with a aM co-twin exhibited superior spatial ability, possibly due to the in utero exposure to the androgens produced by their co-twin (Cole-Harding et al., 1988). On the contrary, aF with Turner syndrome, who in general have lower androgen levels usually demonstrate cognitive deficits in spatial ability (Nijhuis-van der Sanden et al., 2003). Likewise, the complete androgen insensitivity syndrome (CAIS) characterizes individuals with a 46XY karyotype, undescended testes, normal to high levels of testosterone and a birth-assigned female phenotype due to lack of functional androgen receptors (Imperato-McGinley et al., 1982). Studies have shown that individuals with CAIS perform worse on spatial tasks compared to both their aM and non-CAIS aF counterparts (Imperato-McGinley et al., 1991). Whether androgens have activation effects that enhance spatial ability in aM and aF with functional androgen receptors cannot be oversimplified and remains less conclusive (Pintzka et al., 2016; Puts et al., 2010; Spritzer et al., 2011). Indeed, there seems to be different and more complex mechanisms that underlie the potential enhancing effect of androgens on spatial ability in aF with functional androgen receptors. However, there is some evidence that high testosterone levels improve specific tasks of spatial ability including mental rotation ability, route-learning and performance of a block design task (Pintzka et al., 2016; Spritzer et al., 2011).
| Author, Year       | Country             | Study design     | Sex  | Type of treatment                                                                 | Study population, N (Exposed to treatment) | Age at first cognitive assessment (mean ± SD) | Follow-up (months) | Cognitive domains assessed |
|-------------------|---------------------|------------------|------|-----------------------------------------------------------------------------------|---------------------------------------------|---------------------------------------------|-------------------|--------------------------|
| Van Goozen, 1995  | The Netherlands     | cohort           | aF   | IM 250 mg/2 weeks or PO 2 x 40 mg/day androgen                                    | 22                                          | 25.7 (range 18-49)                           | 3                 | VM, VR, VSA               |
| Miles, 1998       | United Kingdom      | cross-sectional  | aM   | 4.47 mg/day estrogens or (2.5 mg estrogens and 5 mg progesterone) or (5 mg estrogens and 100 mg anti-androgen) | 59 (29)                                     | 34.8 ± 10.2                                 | NR                | VM, VR, VWM, WM, VSA      |
| Slabbe (koorn), 1999 | The Netherlands    | cohort           | aM   | PO 2 x 50 μg/day estrogen and PO 2 x 50 mg/day anti-androgen                       | 20                                          | 29.1 ± 8.0                                  | 12                | A, MC, VM, VR, VSA        |
| Friedman, 2000    | USA                 | cross-sectional  | aF   | IM 250 mg/2 weeks androgen                                                        | 25                                          | 26.0 ± 7.7                                  | 10                | A, MC, VM, VR, VSA        |
| Van Goozen, 2002  | The Netherlands     | cohort           | aM   | PO 2 x 0.05 mg/day or 0.10 mg/day estrogen and PO 2 x 50 mg/day anti-androgen     | 22                                          | 31.4 ± 10.8                                 | 3.5               | MC, VSA                  |
|                   |                     |                  | aF   | IM 2 x 250 mg/2 weeks or 100 mg/2 weeks or PO 200 mg/day anti-androgen           | 19                                          | 26.2 ± 7.5                                  | 3.5               | MC, VSA                  |
| Haraldsen, 2005   | Norway              | cohort           | aM   | PO 50 μg/day estrogen                                                             | 12                                          | 26.7 ± 5.9                                  | 12                | C, VM, VR, VWM, VSA       |
| USA               |                     |                  | aM   | IM 180 μg/day estragons                                                          | 21                                          | 26.7 ± 5.9                                  |                   | C, VM, VR, VWM, VSA       |
| Miles, 2006       | United Kingdom      | cohort           | aF   | IM 180 μg/3 weeks estragons                                                        | 10                                          | 35.2 ± 10                                   |                   | C, VM, VR, VWM, VSA       |
| Gómez-Gil, 2009   | Spain               | cohort           | aF   | IM (100-200 mg/2-4 weeks) or TD (5-10 g/day) androgen                            | 14                                          | 27.4 ± 9.3                                  | 6                 | VWM, ViWM                 |
| Schöné, 2010      | Germany             | cross-sectional  | aM   | PO estrogen or PO estrogen and anti-androgen for 0.5-2 years (mean duration 1.14 years) | 22 (11)                                     | 36.2 ± 9.8                                  | NR                | VR, VSA                  |
| Burke, 2016       | The Netherlands     | cohort           | aF   | 250 mg/ml/2 weeks or 12 weeks testosterone ester mixture                        | 21                                          | 16.0 ± 0.8                                  | NR                | VSA                      |

Abbreviations: aF, assigned female; aM, assigned male; SD, standard deviation; PO, per os; IM, intramuscular depot; TD, transdermal; NR, not reported; A, Attention; MC, motor coordination; C, Computation; VM, Verbal memory; VR, Verbal reasoning; WM, Working memory; VWM, Verbal working memory; ViWM, Visual working memory; VSA, visuospatial ability
In the same context and consistently with recent studies, the present meta-analysis provides some evidence for a sex differential effect of hormone treatment on cognition confined mainly to visuospatial ability among aF (Jäncke, 2018), which seems biologically plausible. Indeed, cognitive function in transgender individuals naive to gender-affirming treatment seems to be more congruent with their gender identity than their birth-assigned sex, creating, thus, a restricted potential for change (Nawata et al., 2010; Rametti et al., 2011; Simon et al., 2013; Zhou et al., 1995). Taking also into account neurogenesis, the most plastic regions of human brain are the subventricular (SVZ) and the subgranular zone (SGZ) of the hippocampus (Bacigaluppi et al., 2020; Kolb et al., 2017). Recent research has shown a strong correlation between cells in the hippocampal formation and spatial ability (Hartley et al., 2014; Laube et al., 2020), which may at least partially explain why this cognitive domain may be more prone to alteration. Of note is the trend towards statistically significant enhancement in visuospatial ability among aM transgender individuals following gender-affirming hormone treatment. Oestrogens are not currently considered to have a major role in the masculinization of the human brain, but data are scarce (Swaab, 2004). There are indications from lower mammals that estrogenic receptors are involved in the masculinization of neural circuits in brain areas important for sexual behaviour (Kudwa et al., 2006; McCarthy, 2008), as well as that oestrogens may upregulate the expression of androgen receptors (McAbee and Doncarlos, 1999). A recent study on transgender individuals supports the involvement of estrogen receptors together with the androgen receptor in gender development (Fernandez et al., 2018). Moreover, in human prostate cells, 17β-estradiol, but not diethylstilbestrol was found to be a natural ligand for androgen receptor and may play an essential role for the development of the male reproductive system (Yeh et al., 1998). Given the complex physiological effects of steroid hormones on brain function and the scarcity of research on the effects of prenatal or pubertal testosterone and oestrogen levels in aM individuals, the present results, especially regarding the weak and non-statistically significant enhancement in visuospatial ability among aM following hormonal treatment need to be replicated in future studies to allow firm conclusions to be drawn.

Regarding other cognitive domains beyond visuospatial ability, the absence of verbal cognitive enhancements besides verbal working memory among aM transgender individuals following hormonal treatment might be due to the absence of circulating progesterone, which differentiates them from their cisgender aF counterparts (Maki and Henderson, 2012; Nguyen et al., 2018; Sherwin and Grigorova, 2011; Shumaker et al., 2003). Indeed, exogenous progesterone seems to be
associated with improved neuropsychological measures in verbal memory compared to placebo (Berent-Spillson et al., 2015; Sherwin and Grigorova, 2011). In addition, recent studies suggest that sex hormones do not globally modulate verbal memory or forgetting, but selectively affect cue-specific processing (Kerschbaum et al., 2017; Resnick et al., 2006); specifically, there is some evidence that progesterone may enhance the inhibitory mechanism in item-context binding in forget-cued young aF individuals (Kerschbaum et al., 2017).

To this end, although the results of the present meta-analysis confirm current evidence that gender-affirming hormone treatment enhances specific cognitive domains in transgender individuals congruent with their gender identity (Nguyen et al., 2018), these stipulations merit cautious interpretation. Future studies are needed to address the inherent limitations of to-date literature, including the cross-sectional design, the limited follow-up times and the lack of adjustment for other potential confounders, such as prior hormonal treatment modalities. Indeed, the short follow-up period (maximum of 12 months) may have hampered the potential for a statistically significant difference in less plastic cognitive functions to be shown. In particular, the potential adverse long-term effects of estrogenic depletion on specific executive areas of cognition, such as memory and attention should be targets of future longitudinal studies with longer follow-up given that transgender individuals are usually under long-term gender-affirming hormone administration (Shanmugan and Epperson, 2014; Shanmugan et al., 2017).

4.3. Strengths and limitations

A major strength of this first meta-analytic attempt lies in its sound methodologic approach according to current guidelines. Following an independent dual screening of the existing literature and rigorous communication with the authors of potentially eligible articles, the study participants contributing information in main analyses were more than 200 aM and 150 aF, with no significant heterogeneity noticed among included studies. Moreover, separate meta-analyses by study design were undertaken, as well as meta-regression analyses, which showed no significant impact of the main potential effect modifiers including publication year, average follow-up period, country of origin and mean age on the associations of interest. However, it must be noted that only one study included adolescents while most individuals included in the present meta-analysis were at the mid-20 s to 30 s. We can thus not generalize our findings in the younger group of transgender people who are increasingly seeking gender-affirming treatment during the last decade.

Our findings should be interpreted in view of inherent limitations involving the small number of published studies, which limited the statistical power to conduct sub-analyses and the variable study periods, though meta-regression did not show any significant effect of publication year on the observed associations. Likewise, despite the absence of significant between-study heterogeneity, our results may have been hampered by differential exposure and outcome ascertainment bias due to the heterogeneous gender-affirming treatment
modalités (different regiments, dosages and frequencies of steroid hormonal treatment; sex reassignment surgery) and the diverse cognitive assessment tests implemented by each study. In addition, the majority of included studies lacked information on potential confounding factors, such as history of previous treatment modalities prior to the gender-affirming hormone protocol including the type, dosage and frequency of medications administered. Though the majority of eligible studies were of cohort design and high quality, the cross-sectionally derived summary effect estimates should be interpreted with caution given the potential for inverse causality. Moreover, although meta-regression did not show a significant modifying effect of the diversity between-study follow-up periods on the observed associations, the short follow-up in all studies remains an issue of concern, which may have not allowed a statistically significant change in cognitive function to be shown, beyond visuospatial ability. Furthermore, the assessment of publication bias was not feasible due to the small number of study arms. Of note, the majority of studies were conducted in Europe pointing to the need for more ethnically diverse populations in future studies to allow generalizable conclusions to be made. Lastly, gender non-binary or gender non-conforming individuals who do not identify as transgender were absent from to-date published literature; future research should target these populations to assess how hormones to develop more masculine or feminine sexual secondary characteristics might also affect their cognitive performance.

4.4. Conclusions

The present meta-analysis suggests a potentially enhancing effect of gender-affirming hormone treatment on cognitive function in transgender young adult individuals congruent with their gender identity than birth-assigned sex. Specifically, the existing body of research provides epidemiologic evidence that supports the enhancing role of post-pubertal steroid hormonal administration in visuospatial ability in aP individuals. Given the inherent limitations and methodological obstacles of current literature derived from the older studied populations and short follow-up, as well as the interference of many potential confounders, these results are by no means definite, but they do warrant further investigation on an international basis. Longitudinal properly designed and culturally diverse studies with larger and homogeneous samples, longer follow-up periods and control for all intermediate covariates including history of prior treatments are needed to allow firm conclusions to be drawn. To this end, the present results, if confirmed in future research, could have a significant clinical impact for health care professionals and health policy planners. Finally, further gender-affirming research should focus on the effects on younger transgender individuals, as well as on the full spectrum of diversity in gender identity and gender expression beyond the binary to allow assessment of the potential health-related issues along the entire gender spectrum.

Role of the funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations of Competing Interest

None.

Acknowledgments

We would like to express our gratitude to the clinical neuropsychologists Thomas Höljö and Johan Isaksson for sharing their expertise in categorizing the variable cognitive tasks used in the literature in specific cognitive domains. Moreover, we acknowledge Ilias Sinanidis for his assistance in data abstraction and quality assessment of the eligible studies. We also thank all authors who replied to the request for additional data.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2020.104721.

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