Journal of Psychosomatic Research 83 (2016) 57–64

Contents lists available at ScienceDirect

Journal of Psychosomatic Research

Psychosocial well-being in Dutch adults with disorders of sex development

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ARTICLE INFO

Article history:
Received 16 October 2015
Received in revised form 4 March 2016
Accepted 10 March 2016
Available online xxxx

Keywords:
Disorders of sex development (DSD)
Psychosocial well-being
Health related quality of life
Self-esteem
Emotional problems
Fatigue

ABSTRACT

Objective: Atypical sex development is associated with psychosocial vulnerability. We investigated psychosocial well-being in individuals with disorders of sex development (DSD) and hypothesized that psychosocial well-being was related to degree of genital atypicality at birth.
Methods: 120 male ($n = 16$) and female ($n = 104$) persons with DSD, aged 14–60 years, participated in a follow-up audit on psychosocial well-being. They were stratified in: women with 1) 46,XY and female genitalia, 2) 46,XY or 46,XX and atypical genitalia, and 3) men with 46,XY and atypical genitalia. We used the Illness Cognition Questionnaire (ICQ), Checklist Individual Strength (CIS8R), TNO-AZL Quality of Life questionnaire (TAAQOL), Adult Self-Report (ASR), and the Rosenberg Self-Esteem Scale (RSES).
Results: Data were compared to reference groups. Participants generally were coping well with DSD (ICQ). Women with DSD reported elevated levels of fatigue (CIS8R) and slightly more attention and memory problems (TAAQOL, ASR). Women with atypical genitalia reported more emotional and behavioral problems. On the ASR Rule-breaking Behavior and Antisocial Personality scales, these women had similar scores as reference men. Women with DSD reported a higher self-esteem (RSES). No differences in psychosocial well-being were found between men with DSD and reference men.
Conclusion: Individuals with DSD across all diagnostic groups generally reported a good psychosocial well-being. The results further suggest involvement of prenatal androgens in the development of personality traits related to assertiveness and egocentricity. We recommend that individuals with a DSD and their families are involved in decision-making processes and have access to multidisciplinary care.

1. Introduction

In individuals with disorders of sex development (DSD) the development of chromosomal, gonadal, and/or anatomic sex is atypical [1]. It is assumed that this incongruence puts them in a vulnerable position in society [2]. Current clinical management strategies therefore will include advice for early gender assignment, genital corrections, and hormonal treatments [1]. Lately, these early interventions have raised debate: it has been argued that they reflect society's intolerance to variance in sex and gender and major decisions are made without consent of children themselves [3–6]. It has been suggested that postponement of gender assignment and genital surgery until the child is old enough to decide him/herself will benefit the child's well-being [7]. Randomized controlled comparison of the current treatment policy and the policy of delayed interventions is highly valued [8] but is difficult to conduct. The majority of parents living in Western countries choose gender assignment and genital surgery in early childhood [9–11].

Outcome studies on psychosocial well-being have been conducted. Due to differences in applied methodology and measures, findings are difficult to compare and show inconsistencies. These studies have mainly been carried out in females and focused on gender identity [12–18], sexual quality of life [19–23], and (psycho)sexual functioning [24–32], while studies on quality of life [33], social participation, self-esteem, and emotional problems are scarce. Studies addressing health related quality of life (HRQoL), emotional distress, and psychopathology in women with 46,XX congenital adrenal hyperplasia (CAH) revealed inconclusive outcomes, from reduced to a better HRQoL [20,34–36], and from no substantial emotional distress to increases in emotional problems [28, 37–40]. Women with complete androgen insensitivity syndrome (CAIS)

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http://dx.doi.org/10.1016/j.jpsychores.2016.03.005
0022-3999/

reported to function psychologically well or even better than reference groups [20,41]. In individuals with partial androgen insensitivity syndrome (PAIS), disorders in the biosynthesis of androgens, or gonadal dysgenesis, mental health problems have been reported [42], but findings had not been replicated in another study [16].

A few studies have been conducted in men and focused on sexual functioning [29]. Men with 46,XY CAH suffer from adrenal problems and testicular adrenal rest tumors and its consequences [43,44]. These men reported more negative emotions [45], anxiety and depression [40], and psychiatric morbidity [46,47]. Impairments in subjective health status have been reported [40,48], but also a favorable health status compared to the general population [36].

In DSD there is a great variety in genital development between and within different diagnostic groups. In the current study we evaluated psychosocial well-being in relation to gender of rearing and degree of genital atypicality in Dutch individuals with DSD. In their prenatal development, persons with DSD have been exposed to atypical levels of androgens. We hypothesized that persons with DSD who underwent an atypical prenatal development leading to physical atypicality are more vulnerable to experiences that negatively affect their psychosocial well-being compared to persons with typical female or male genitalia [2].

2. Methods

2.1. Study design

The present study was embedded in a national follow-up audit on sexual well-being, gender identity development, and psychosocial well-being in persons with DSD [24,25,29,30]. The study protocol was in line with the World Medical Association declaration of Helsinki and was approved by the boards of the ethical committees of the three medical centers that joined the study [49]. Data collection was carried out between 2007 and 2012. The Dutch patient support groups were involved in the study; the study was presented and discussed with them, findings were presented at gatherings and published in the organizations' newsletters and the scientific publications were provided to them.

2.2. Participants

All participants consulted the DSD Teams from Erasmus Medical Center Rotterdam ($n = 67$), Radboud University Nijmegen Medical Center ($n = 38$), or VU Medical Center Amsterdam ($n = 15$). Persons with a clinically or molecularly proven DSD diagnosis were included. Excluded were patients with 1) intellectual disabilities, 2) a genital anomaly in combination with features suggestive of malformation syndromes [50], 3) anatomical mal-development of the genitalia and abdomen with normally developed and well-functioning gonads (e.g. cloacal/bladder malformations), 4) Klinefelter 47,XXY and Turner 45,X non-mosaic types as these patients suffer from somatic and psychological characteristics typical for these syndromes [51,52], and 5) Mayer–Rokitansky–Küster–Hauser syndromes as these women have normal ovarian development and function. Participants were between 14 and 60 years old, of which four persons were aged under 17 and three approached their 18th birthday.

All participants received written additional study information and gave their informed consent.

2.3. Procedure

To examine the influence of atypical prenatal action of testosterone and its related genital atypicality on psychosocial well-being, participants were initially divided into four subgroups according to karyotype, gender of rearing, and degree of genital masculinization [25]: 1) the 46,XY FG women group, $n = 35$. This group comprised women with 46,XY karyotype with normal appearing female external genitalia; women with a normally sized clitoris, normally developed labia minora and majora, vaginal dysplasia and gonads in the abdomen or groins. 2) The 46,XY AG women group, $n = 27$. This group comprised women with 46,XY karyotype with various degrees of virilization of the external genitalia; women with an enlarged clitoris, partially or completely fused labia, vaginal dysplasia and gonads in the abdomen or groins. 3) The 46,XX AG women group, $n = 42$. This group comprised women with 46,XX karyotype and CAH women with various degrees of virilization of the external genitalia; ambiguous genitalia such as an enlarged clitoris, partially or completely fused labia, small introitus, or confluence of the vagina and urethra. 4) The 46,XY AG men group, $n = 15$. This group comprised men with 46,XY karyotype with various degrees of undervirilization of the external genitalia; i.e. proximal hypospadias and unilateral/bilateral cryptorchidism. In this group we also included one person with 46,XX CAH, who had been assigned and raised in the male gender from birth onwards (CAH was identified at age 19).

We initially tested the justification of our grouping method for intergroup comparisons by examining between-group differences on all outcome measures. Results revealed significant differences in scoring between 46,XY FG women and 46,XY and 46,XX AG men on the one hand, and 46,XY AG women and 46,XX AG women on the other hand. Subsequently we tested for differences between 46,XY AG women and 46,XX AG women, but no significant differences were found. As no contraindications were found for combining the 46,XY AG women and 46,XX AG women groups, we combined these groups for further analyses. Table 1 summarizes participants' characteristics and their diagnoses.

2.4. Instruments

2.4.1. ICQ

The Dutch 18-item Illness Cognition Questionnaire (ICQ) measures cognitions in chronic diseases [53]. It contains three subscales that measure helplessness (e.g. 'My illness limits me in everything that is important to me'), acceptance (e.g. 'I have learned to live with my illness'), and perceived benefits (e.g. 'Dealing with my illness has

Table 1
Diagnostic information of participant subgroups.

Raised as	*Females*		*Males*
	46,XY Female genitalia ($n = 35$)	46,XY or 46,XX Atypical genitalia ($n = 69$)	46,XY or 46,XX Atypical genitalia ($n = 16$)
Diagnosis	**46,XY** 22 CAIS 14 Complete GD	**46,XY** 2 Partial GD 8 17β3 HSD 5 PAIS 2 Hypomasculinisation e.c.i. 3 Leydig cell hypoplasia 1 17,20 LD 1 NR5A-1 **45,X/46,XY** 4 Mixed GD **46,XX/46,XY** 1 Mixed GD **46,XX/46,XY/46,XXY** 1 Mixed GD **46,XX** 39 CAH, CYP21A 2 CAH, 11B1	**46,XY** 2 PAIS 6 Severe hypospadias e.c.i 1 Hypomasculinisation e.c.i. **45,X/46,XY** 3 Mixed GD **46,XX/46,XY** 1 Ovotesticular DSD **46,XX** 1 CAH 2 Ovotesticular DSD

Note. Abbreviations: CAIS = Complete androgen insensitivity syndrome, GD = Gonadal dysgenesis, 17β HSD = 17β hydroxysteroid dehydrogenase deficiency type 3, PAIS = Partial androgen insensitivity syndrome, e.c.i = unknown cause, 17,20 LD = 17,20 Lyase deficiency, NR5A-1 = NR5A-1 gene mutation, CAH = Congenital adrenal hyperplasia, CYP21A = 21-hydroxylase deficiency, CYP11B1 = 11β-hydroxylase deficiency.

made me a stronger person') on a 4-point Likert scale ranging from 1 (*not at all*) to 4 (*completely*). The instrument has good psychometric properties [53]. Reference data are available from different Dutch patient groups with chronic conditions that impedes independent daily functioning and self-care. We compared persons with DSD with patients with fibromyalgia (24 men, 348, women) as this reference group matched best to persons with DSD with respect to independence in daily functioning. [54].

2.4.2. CIS8R

The 8-item Checklist Individual Strength-Subjective Fatigue scale (CIS8R) measures experienced fatigue [55–57]. Higher scale scores indicate more fatigue-related problems. The normal range includes scores <27, increased fatigue includes scores 27–35, and severe fatigue includes scores >35. The instrument shows good psychometric properties [57]. A reference sample from the Dutch population was used in statistical analyses.

2.4.3. TAAQOL

The 45-item TNO-AZL Quality of Life (TAAQOL) questionnaire is a Dutch generic measure of HRQoL in medical research [58]. Items inform about the incidence of physical, psychological or social problems on different domains and are scored on a 4-point Likert scale, ranging from *never* to *often*. If a problem is reported, the subject rates the emotional reaction to the problem on a 4-point Likert scale, ranging from *bad* to *alright*. Higher scores indicate a better HRQoL. Because of the multidimensional nature of the instrument, no total score is calculated. For this study, scales on pain and motor functioning were omitted as patients with DSD do not suffer from pain and impairments as a result of their medical condition. The TAAQOL has good psychometric properties. Reference data are available for a large sample of the general Dutch population [59].

2.4.4. ASR

The 131-item Adult Self-Report (ASR) measures emotional and behavioral functioning in adults aged 18 and older [60]. It comprises eight scales for emotional and behavioral problems and six scales assessing criteria [61] for psychiatric diagnoses according to the DSM 5 [62]. Items are scored on a 3-point Likert scale, ranging from 0 (*not true*) to 2 (*very true or often true*). Cut-off scores help to identify persons who score in clinical ranges and are at risk to develop severe emotional and behavioral problems [60]. Higher scores indicate more problems. Satisfactory psychometric properties have been determined for the original ASR. Large Dutch male and female samples were used as reference groups [63].

2.4.5. RSES

The Rosenberg Self-Esteem Scale (RSES) is a 10-item self-report measure on self-esteem [64,65]. The total score reflects the degree of global self-esteem, which can be divided in Self-competence (5 items) and Self-liking (5 items) [66]. Items are rated on a 4-point Likert scale, ranging from 1 (*strongly disagree*) to 4 (*strongly agree*). The Dutch translation of the RSES has good psychometric properties. Self-esteem scores by individuals with DSD were compared to those found in a Dutch population study [65].

Participants could refuse filling out questionnaires or answering specific questions. Only completely filled out scales or questionnaires were included in the study; hence the numbers of participants who filled out questionnaires differed among questionnaires.

3. Statistical analysis

Before statistical analyses we evaluated the internal consistencies of the abovementioned measures for our sample using Cronbach's alpha. For most questionnaires, internal reliability values were good (Cronbach's α above .70). For three ASR-scales, internal reliability values were acceptable (Rule-breaking Behavior, Thought Problems and Antisocial Personality Problems; Cronbach α's respectively .64, .66, and .66).

For categorical variables, between-group differences were tested using Chi-square tests or (in case of small samples) Fisher's exact tests for independent samples. Kolmogorov–Smirnov and Shapiro–Wilk testing revealed skewed data distributions for the large majority of scales in all groups, hence between-group differences in continuous data were examined using Mann–Whitney *U* tests (two groups) or Kruskal–Wallis tests (three or more groups). In case of significant between-group differences, results were followed up by post-hoc Mann–Whitney testing, applying Bonferroni corrections to adjust for multiple testing. For the ICQ and CIS8R, comparisons with reference sample means were executed using one-sample *t*-tests. For RSES, comparisons with reference sample medians were executed using Wilcoxon signed-rank tests.

Differences were considered significant at $p < .05$ (two-sided). All statistical analyses were conducted using IBM SPSS Statistics version 21.0.

4. Results

4.1. Participant characteristics

Table 2 summarizes socio-demographic characteristics. Groups did not differ in median age ($p = .49$), ancestry ($p = .09$), marital status ($p = .27$), educational level ($p = .52$) or vocational status ($p = .65$).

Reasons for non-response remained unknown; most no-participation forms were not returned or were not filled out completely. Responders and non-responders did not differ with respect to diagnosis, medical treatment, age, living in urban or rural areas, or medical center [25,29,30].

Table 2
Socio-demographic characteristics of participant subgroups.

Raised as	*Females*		*Males*
	46,XY Female genitalia ($n = 35$)	46,XY or 46,XX Atypical genitalia ($n = 69$)	46,XY or 46,XX Atypical genitalia ($n = 16$)
Median age in years (range)	24 (15–49)	27 (15–60)	25 (14–59)
Marital status (%)			
Single	48.6	46.4	68.8
Relationship	51.4	53.6	31.3
Ancestry (%)			
Dutch	85.7	73.9	56.3
Immigrant[1]	2.9	13	31.3
Mixed Dutch - Immigrant	5.7	2.9	–
Not specified	5.7	10.1	12.5
Educational level (%)			
Low	2.9	11.6	–
Middle	68.6	62.3	68.8
High	28.6	26.1	31.3
Children (%)			
No children	85.7	88.4	87.5
Biological children	–	4.3[2]	6.3[3]
Stepchildren	5.7	2.9	6.3
Adopted/foster	5.7	2.9	–
Not indicated	2.9	1.4	–
Vocational status (%)			
Student	28.6	23.2	37.5
Unemployed	8.6	8.7	12.6
Working	60	65.2	50.1
Not indicated	2.9	2.9	–

[1] Immigrant = European, Asian, African, Arabic non-specified, Turkish, Moroccan, Kurdish, Indian, Chinese.
[2] Women with CAH.
[3] Man with severe hypospadias.

Table 3
Mean scores and standard deviations on illness cognitions (ICQ).

Raised as		*Females*		*Males*
	Reference group ($n = 372$)	46,XY Female genitalia ($n = 34$)	46,XY or 46,XX Atypical genitalia ($n = 68$)	46,XY or 46,XX Atypical genitalia ($n = 15$)
Helplessness	12.90 (3.87)	8.26 (2.96)[2]	8.91 (3.40)[2]	11.00 (5.26)
Acceptance	15.35 (4.14)	18.37 (4.14)[2]	18.45 (4.23)[2]	17.14 (5.36)
Perceived benefits	14.62 (4.28)	12.00 (4.58)[1]	13.84 (5.03)	11.87 (5.15)

[1] Comparison with reference group, $p < .01$.
[2] Comparison with reference group, $p < .001$.

4.2. Illness cognitions

Details on illness cognitions (ICQ) can be found in Table 3. Women with DSD (FG and AG) reported less feelings of helplessness ($p < .001$) and had accepted their condition better ($p < .001$) than the reference group of fibromyalgia patients. Compared to the reference group, women with 46,XY FG perceived less disease benefits ($p = .002$), whereas women with 46,XY or 46,XX AG perceived disease benefits similar to the reference group ($p = .22$). There were no differences between men with DSD and the reference group.

4.3. Subjective fatigue

Table 4 summarizes findings on fatigue (CIS8R). Increased fatigue was reported by 17.8% of women with DSD (FG and AG) and severe fatigue by 27.7%. Reported subjective fatigue was significantly higher than the reference group (respectively $p = .004$ and $p < .001$). Fatigue was not correlated with age ($p = .83$). There were no differences between men with DSD and the reference group ($p = .10$).

4.4. Health related quality of life

Details on the TAAQOL can be found in Table 5. In general, participants reported few problems in HRQoL. Women with DSD tended to report more positive emotions ($p = .046$) and a trend towards better social functioning ($p = .05$) than reference women. Only on the cognitive functioning scale, which refers to affected memory and attention, women with DSD reported significantly more problems (46,XY FG women: $p = .002$; 46,XY or 46,XX AG women: $p < .001$). No differences were found between individuals with DSD and the male and female reference groups on the remaining TAAQOL scales.

4.5. Emotional and behavioral problems and psychopathology

Details on the ASR can be found in Table 6. Median scores were below the clinical cut-off score for psychopathy ($T = 70$) for all groups on all variables, meaning that observed differences between groups are not necessarily clinically relevant. Analyses revealed that women born with atypical genitalia reported significantly more emotional and behavioral problems than reference women on several syndrome and DSM- scales. As Table VI shows, these women reported significantly more problems than reference women on the Rule-breaking Behavior scale ($p < .01$) and DSM-scale Antisocial Personality Problems ($p < .001$). For men and women different reference data are available. As women with atypical genitalia had been prenatally exposed to elevated levels of effective androgens, we assumed that their higher scores on these particular scales could be related to a masculinizing behavioral effect of this exposure. When we used the male scoring norms to compare our data with, the significances between scores of the women with atypical genitalia and reference men indeed disappeared; Rule-breaking Behavior: $p = .96$ and Antisocial Personality Problems: $p = .15$. There were no differences between men with DSD and reference men.

4.6. Self-esteem

Results on self-esteem (RSES) can be found in Table 7. Compared to reference women, women with DSD (FG and AG) reported significantly higher global self-esteem ($p < .001$) and self-liking ($p = .002$). Women with 46,XY FG felt more self-competent ($p = .014$) as well. Their median score on global self-esteem was close to that of reference men. No differences were found between men with DSD and reference men.

5. Discussion

This study aimed to investigate psychosocial well-being in Dutch individuals with DSD. Overall, we conclude that participants reported good psychosocial well-being; they generally reported a good HRQoL, no serious emotional problems, a high self-esteem, and seemed to cope well with DSD compared to reference groups. In a recently published review [67] on this subject, seven out of 10 studies reported a (mildly) affected psychosocial well-being, in three studies such changes were not reported. Our findings are in line with these latter studies; we did not observe differences in psychosocial well-being between adults with DSD and reference groups. A few differences were found between women with 46,XY FG, 46,XY or 46,XX AG DSD and men with DSD. How can

Table 4
Mean scores and standard deviations on subjective fatigue (CIS8R).

Raised as		*Females*		*Males*
	Reference group ($n = 53$)	46,XY Female genitalia ($n = 35$)	46,XY or 46,XX Atypical genitalia ($n = 66$)	46,XY or 46,XX Atypical genitalia ($n = 15$)
Mean (*SD*)	17.3 (10.1)	23.8 (12.4)[1]	27.9 (14.0)[2]	23.3 (13.0)
		n (%)	*n* (%)	*n* (%)
Normal fatigue		23 (65.7)	32 (48.5)	10 (66.7)
Increased fatigue		5 (14.3)	13 (19.7)	1 (6.7)
Severe fatigue		7 (20)	21 (31.8)	4 (26.7)

Note. Abbreviations: *SD* = standard deviation.
[1] Comparison with reference group, $p < .01$.
[2] Comparison with reference group, $p < .001$.

Table 5
Median scores and ranges of scores on health-related quality of life (TAAQOL).

Raised as	*Females*			*Males*	
	Reference women ($n = 2396$)	46,XY Female genitalia ($n = 35$)	46,XY or 46,XX Atypical genitalia ($n = 65$)	46,XY or 46,XX Atypical genitalia ($n = 14$)	Reference men ($n = 1990$)
Cognitive functioning	93.8 (0–100)	75 (6.3–100)[1]	68.8 (12.5–100)[2]	87.5 (25–100)	93.8 (0–100)
Sleep	75 (0–100)	87.5 (31.3–100)	81.3 (6.3–100)	87.5 (0–100)	87.5 (0–100)
Social functioning	87.5 (0–100)	93.8 (37.5–100)	100 (25–100)	87.5 (31.3–100)	87.5 (0–100)
Daily activities	93.8 (0–100)	93.8 (0–100)	87.5 (0–100)	90.6 (43.8–100)	100 (0–100)
Sexuality	100 (0–100)	100 (0–100)	100 (0–100)	100 (0–100)	100 (0–100)
Vitality	66.7 (0–100)	75 (16.8–100)	66.7 (0–100)	66.7 (25–91.7)	75 (0–100)
Positive emotions	66.7 (0–100)	66.7 (25–100)	66.7 (33.3–100)	66.7 (0–91.7)	66.7 (0–100)
Depressive emotions	83.3 (0–100)	83.3 (25–100)	83.3 (41.7–100)	83.3 (33.3–100)	83.3 (0–100)
Aggressive emotions	88.9 (0–100)	100 (66.7–100)	88.9 (11.1–100)	100 (55.6–100)	100 (0–100)

[1] Comparison with reference women, $p < .01$.
[2] Comparison with reference women, $p < .001$.

this be explained? The median age in our sample was 26 years; the majority of participants was thus born after 1980. From the end of the 1970's onwards, clinical management in the Netherlands is executed by health workers with expertise on medical and psychosocial aspects of DSD [68–71]. Patients were referred to such teams directly after identification of sexual incongruence.

Despite their overall good psychosocial well-being, participants reported some specific complaints and less positive areas of functioning. A significant proportion of women experienced increased fatigue, which might be related to their atypical hormonal milieu. Fatigue is a well-known complaint of menopausal women and is frequently reported by young women with premature loss of gonadal functioning who take hormone replacement therapy [72]. All women with 46,XY karyotype in this study had undergone gonadectomy in childhood or puberty to prevent malignancies. Women with CAH reported fatigue too. Fatigue is a common complaint in adrenal insufficiency and is explained by dysfunction of the hypothalamic–pituitary-adrenal (HPA) axis [73]. Further research on the relationship between fatigue and HPA-axis dysfunction will elucidate the influence of gonadal hormones on vitality.

Women with DSD, in particular women born with atypical genitalia, reported problems in attention and memory (TAAQOL, ASR). Mild impaired attention and memory might be related to heightened levels of fatigue or the influence of glucocorticoids. Browne et al. observed reduced working memory performance in children with CAH [74] and related their findings to glucocorticosteroid abnormality due to postnatal

Table 6
Median and range of *T*-scores on emotional and behavioral problems (ASR).

Raised as	*Females*				*Males*	
	Reference women ($n = 1206$)	46,XY Female genitalia ($n = 32$)	46,XY or 46,XX Atypical genitalia, scored female ($n = 63$)	46,XY or 46,XX Atypical genitalia, scored male ($n = 63$)	46,XY or 46,XX Atypical genitalia ($n = 12$)	Reference men ($n = 1036$)
Syndrome scales						
Anxious/depressed	52 (50–96)	51.5 (50–72)	54 (50–74)	56 (50–75)[6]	53 (50–81)	50 (50–89)
Withdrawn	51(50–97)	51 (50–80)	56 (50–80)[1]	54 (50–80)[4]	54 (50–90)	51 (50–93)
Somatic complaints	54 (50–100)	52 (50–86)	54 (50–84)	57 (50–85)[6]	51 (50–60)	51 (50–85)
Thought problems	50 (50–100)	51 (50–80)	54 (50–75)[3]	54 (50–75)[6]	51 (50–65)	50 (50–85)
Attention problems	53 (50–91)	56.5 (50–79)	57 (50–85)[3]	57 (50–81)[6]	55.5 (50–64)	54 (50–100)
Aggressive behavior	52 (50–98)	52.5 (50–68)	53 (50–69)[3]	53 (50–69)[6]	51.5 (50–70)	51 (50–100)
Rule-breaking behavior	52 (50–100)	51 (50–73)	56 (50–72)[2]	54 (50–69)	51 (50–57)	54 (50–87)
Intrusive	50 (50–78)	50.5 (50–73)	51 (50–70)	51 (50–70)	50 (50–58)	51 (50–100)
Internalizing problems	51 (30–93)	48.5 (32–74)	57 (30–80)	59 (30–81)[6]	51.5 (32–78)	48 (30–85)
Externalizing problems	50 (30–99)	51 (32–75)	53 (34–70)[2]	52 (34–70)[4]	47.5 (30–63)	49 (30–82)
Total problems	48 (25–96)	49 (37–77)	53 (34–72)[2]	54 (34–70)[6]	49.5 (26–64)	48 (25–80)
Critical items	52 (50–99)	54 (50–76)	59 (50–71)[3]	59 (50–71)[6]	53.5 (50–67)	51 (50–84)
Substance use						
Tobacco	50 (50–100)	50 (50–68)	50 (50–77)	50 (50–70)	50 (50–67)	50 (50–90)
Alcohol	50 (50–84)	52.5 (50–65)	50 (50–77)	50 (50–71)[6]	50 (50–56)	51 (50–93)
Drugs	50 (50–100)	50 (50–68)	50 (50–73)	50 (50–66)[5]	50 (50–63)	50 (50–100)
Mean substance use	50 (50–86)	52 (50–72)	50 (50–70)	50 (50–63)[5]	50 (50–58)	51 (50–77)
DSM 5-oriented scales						
Depressive problems	52 (50–96)	51 (50–74)	53 (50–74)	55 (50–63)[6]	51 (50–72)	51 (50–84)
Anxiety problems	52 (50–80)	50 (50–70)[1]	51 (50–70)	52 (50–73)[5]	51.5 (50–69)	50 (50–80)
Somatic problems	56 (50–100)	53 (50–84)	55 (50–86)	56 (50–86)[6]	50 (50–60)	52 (50–92)
Avoidant personality problems	53 (50–87)	51 (50–70)	54 (50–80)	55 (50–80)[5]	55 (50–90)	51 (50–90)
AD/H problems	52 (50–98)	54 (50–90)	60 (50–85)[3]	59 (50–80)[6]	54 (50–61)	53 (50–87)
Antisocial personality problems	51 (50–80)	52 (50–66)	54 (50–71)[3]	52 (50–72)	50 (50–61)	51 (50–86)

Note. *T*-scores are standardized scores correcting for age and gender. Clinical cut-off: $T = 64$ for Internalizing, Externalizing, and Total problems scales. $T = 70$ for all other scales.
[1] Comparison with reference women, $p < .05$.
[2] Comparison with reference women, $p < .01$.
[3] Comparison with reference women, $p < .001$.
[4] Comparison with reference men, $p < .05$.
[5] Comparison with reference men, $p < .01$.
[6] Comparison with reference men, $p < .001$.

Table 7
Median scores and range of scores on self-esteem (RSES).

Raised as	*Females*			*Males*	
	Reference women ($n = 125$)	46,XY Female genitalia ($n = 30$)	46,XY or 46,XX Atypical genitalia ($n = 58$)	46,XY or 46,XX Atypical genitalia ($n = 14$)	Reference men($n = 114$)
Total score	30 (19–40)	35.5 (19–40)[2]	33 (22–40)[2]	32 (15–40)	33 (20–40)
Self-competence	16 (10–20)	8 (10–20)[1]	16 (11–20)	16.5 (8–20)	17.5 (10–20)
Self-liking	15 (8–20)	17 (9–20)[1]	16 (9–20)[1]	15.5 (7–25)	15 (10–20)

[1] Comparison with reference women, $p < .05$.
[2] Comparison with reference women, $p < .01$.

glucocorticoid treatment, with levels of glucocorticoids being either too high or insufficient. In Dutch patients born before 1999,[1] salt-wasting crises may have contributed to reduced working memory performance too [20].

In our study, women born with atypical genitalia differed from reference women in some respects: they more often isolated themselves from social activities, reported more thought problems, aggression, rule-breaking and antisocial behaviors. Significances on rule-breaking and antisocial behaviors disappeared when scores were compared to those of reference men. This indicates that these women are more masculine with respect to these personality traits than other Dutch women and may be explained by prenatal elevated levels of testosterone. Such a relationship has been observed before [75–77] and seems to persist into adulthood. Women with 46,XY FG reported no emotional and behavioral problems. They indicated lower levels of anxiety than reference women, which might be related to high levels of self-esteem.

Overall, our study indicates that women born with atypical genitalia experience slightly more psychosocial problems than women born with female genitalia and men with DSD. Women born with atypical genitalia may differ from women born with female genitalia in different areas: they may have more mildly masculinized physical characteristics [78,79], are less feminine in gender behavior and interests [80,81], and underwent more medical interventions early in life [24,25,30]. From preschool age onwards, they have to deal with being slightly different from other girls. Although the women in our study appeared to cope well, these challenges may affect their emotional well-being [82] and clinicians should be aware of their vulnerabilities.

5.1. Strength of the study

The large number of individuals with different DSD conditions in this study enabled us to investigate influences of atypical genital appearance due to atypical prenatal androgen exposure on psychosocial well-being in different subgroups. Follow-up studies in men with DSD are scarce. Our observations contribute to our knowledge, despite small group size.

5.2. Limitations of the study

Some limitations need to be addressed. DSD is an umbrella term that comprises a large variety of diagnoses with a variety of anatomical and biochemical pathways leading to genital ambiguity, resulting in a large variety between participants, even within our study subgroups. We grouped patients on gender and genital atypicality at birth. The abovementioned variety may have affected statistical comparisons.

The response rate was low; about half of the eligible women and even less of the eligible men participated. Non-responders may have a poorer psychosocial well-being or may function better than participants [25,30]. Low response rates are problematic but not uncommon in DSD outcome studies [5,83].

[1] In the Netherlands, population-wide neonatal CAH screening started in 1999

Only 16 men participated. Potential differences between men with DSD and reference groups may have been missed by lack of power to detect small differences in statistical testing. Since 1985, more individuals with DSD are raised as men and nowadays DSD is more often identified in men, particularly in men with more subtle anomalies of the genitalia [84]. Consequently, the number of men available for longitudinal follow-up studies on DSD is currently small. In addition, men were more difficult to reach for the researchers. Information about the study, announcements and calls for participation were also provided by patient support groups. Until recently the Dutch AIS support group was only accessible for women.

5.3. Recommendations for future research

The rareness of DSD, non-representativeness of study groups, differences in applied methodology, small sample sizes and low response rates in DSD outcome studies impede DSD research and may explain the inconsistent study results. One should be cautious to generalize results across diagnoses [22,85].

The generic instruments applied in this study may have overlooked relevant areas for persons with DSD. Studies on psychosocial topics are hampered by the lack of standardized instruments specifically applicable for DSD [86,87]. Previous research showed that disease-specific HRQoL instruments have more power to detect small differences and changes over time and can thus contribute to more effective treatment interventions [88–90]. Disease-specific instruments for young children with DSD are currently being developed [91], but making these instruments cross-culturally applicable will be challenging [87] but advisable to increase sample sizes and carry out methodologically sound research, beyond culture and zeitgeist. A broadened clinical and research agenda is warranted; the findings in this study indicate that a complex interaction among multiple experiences modulate psychosocial outcomes across developmental stages [92].

5.4. Recommendations for clinical management

In addition to medical interventions, individuals with DSD and their families, particularly (parents of) individuals with atypical (small) changes in physical appearance and behavior, need comprehensive care including access to psychological counseling for reinforcement of coping abilities, self-empowerment and a wide range of information resources for both medical and psychological aspects. The heterogeneity in DSD conditions requires different levels of care.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Acknowledgements

We thank all participants who volunteered in this study for their carefulness and efforts. We thank Jan van der Ende and Erwin Birnie

for statistical advices. We thank Ingrid van Slobbe, Joke Dunk, Karen Kwak, Jacqueline Knol, and Hanneke Kempes for their assistance in carrying out the study.

This study has been supported by the Edli Fund (Arianne B. Dessens), FWO Flanders Fund for scientific research (Nina Callens), and Fonds Swart – van Essen (Nita G.M. de Neve –Enthoven).

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