

Quality of Life and Psychological Adjustment of Women Living with 46,XY Differences of Sex Development

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DOI: 10.1111/jsm.12884

ABSTRACT

Background. Progressive care improvement for differences of sex development (DSD), regarding diagnosis communication, psychological, medical and surgical management has been claimed.

Aim of the study. To assess clinical management, quality of life (QoL) and the general psychosocial adjustment of individuals with 46,XY DSD. Some differences related to age at diagnosis are investigated.

Design. Cross-sectional study using standardized questionnaires.

Population. Forty-three Caucasian females with 46,XY DSD (self declared diagnoses: complete androgen insensitivity syndrome, n = 34; complete gonadal dysgenesis, n = 1; 5 α -reductase deficiency, n = 4; Leydig cell hypoplasia, n = 1; unknown diagnosis, n = 3; age years: 31.5 \pm 9.6 [range 18–57 years]).

Setting. University Hospitals.

Methods. Subjects were required to fill in questionnaires (ABCL, WHOQOL, dedicated 17-item questionnaire). Academic and socioeconomic data were compared with those of the Italian population. QoL and psychological data were compared with those of a comparison group (46,XX healthy females: n = 43; age, years: 34.5 \pm 9.7, range 22–51 years).

Results. Present sample of women living with 46,XY DSD were well adapted and were higher achievers than controls, both in educational and professional life. They showed good QoL, but they appeared less satisfied in psychological and social areas. They had borderline mean scores and statistically higher scores than the comparison group for depression, anxiety, internalizing and externalizing problems. Younger persons living with a 46,XY DSD showed better psychosocial adjustment than older ones. Younger women showed lower age at diagnosis communication. Psychological support was more often proposed at the time of diagnosis communication to younger individuals, and they undertook it more frequently than older ones.

Conclusions. Italian people living with 46,XY DSD were well adapted and successful; they reported a good QoL but showed higher degree of psychological distress than the comparison group. Lower psychological distress in younger women could indicate some positive effects of changes in management. **D'Alber-ton F, Assante MT, Foresti M, Balsamo A, Bertelloni S, Dati E, Nardi L, Bacchi ML, and Mazzanti L. Quality of life and psychological adjustment of women living with 46,XY differences of sex development. J Sex Med **;**.***-**.**

Key Words. DSD; Differences of Sex Development; Quality of Life; Psychology, Psychological Adjustment; Hormone Replacement Therapy; Diagnosis Communication

Introduction

Background

The term “disorders of sex development” (DSD) defines a group of congenital conditions in which the development of chromosomal, gonadal, or anatomical sex is atypical [1]. Although considered provisional, this terminology was an attempt to more correctly define a heterogeneous group of rare conditions that had stigmatizing and discriminating names in the past. However, this terminology progressively showed its limits in defining a “variant” of intrauterine human development as a “disorder” [2–5]. Thus, we will use the acronym DSD, standing for “*differences* of sex development.” This term underlines the variability of the human expression of congenital conditions with genetic determinants that are not yet fully known, as well as the best psychological, medical, and surgical approaches to optimize long-term outcomes [1,2,6–12].

Indeed, relevant changes in the management of DSD took place when people with DSD broke the veil of secrecy, blamed the prejudices and paternalism that surrounded their condition [13], and pleaded for a change in its management (<http://isna.org>, <http://accordalliance.org>, <http://aissg.org>, etc.). New information flooded medical congresses and medical practice providing new and innovative points of view [13–15]. Support groups arose all over the world, and the Chicago Consensus started new collaborative work between DSD activists and the medical, surgical, and psychological establishment [1,16]. In Italy, AISIA (Italian Androgen Insensitivity Syndrome support group) has made a great effort to help people, to share information, and to contact medical staff, in order to promote more appropriate DSD management. Among the projects developed by AISIA, there are surveys on quality of life (QoL), emotional, and behavioral well-being, and on opinions about the medical and surgical histories of persons with 46,XY DSD (<http://www.sindromedimorris.org>).

These data are very difficult to collect due to the privacy that must be guaranteed and to the difficulty created by the atmosphere of secrecy and the lack of information that women with DSD suffered from in the past [17,18].

In a peer review, Wisniewski and Mazur [10] found very different data on psychological well-being and quality of life. Mazur et al. [19] assessed the QoL of five persons with 46,XY DSD and reported a general positive QoL in four of them.

Johannsen et al. [20] assessed QoL and mental distress of a mixed sample of 46,XY DSD and 46,XX DSD and found that women with complete androgen insensitivity syndrome (CAIS) had a higher QoL and better psychological outcomes than a control group. Hines et al. [21] studied QoL and general psychological well-being in a group of 22 women with CAIS, showing no statistically significant differences with the matched controls in terms of sexual QoL. Warne [9] investigated a group of 50 46,XY and 46,XX DSD and did not find any differences between the DSD group and the controls, in terms physical and mental health, depression, anxiety, and other aspects of psychological well-being. Problems in sexual confidence and sexual satisfaction were found also by Fliegner et al. [22]. Krupp et al. [23] found that QoL and psychological distress in CAIS were within the average range even though a considerable percentage of individuals were over the cut-off score for clinical relevance. Slijper et al. [24] found a general an overall tendency in people with DSD to develop general psychopathologies. Schützmann et al. [25] (in their sample of 37 persons with different forms of DSD) found high rates of psychological distress. The German network of Disorders of Sex Development [12] studied 439 young, adolescent and adult males and females with different forms of DSD and planned a large clinical evaluation on QoL, gender identity, treatment satisfaction, and other factors related to DSD. In this large-scale project, 47 females with 46,XY DSD were investigated. The preliminary results indicated relevant problems in terms of desire, arousal, and dyspareunia in females with DSD [26], thereby confirming other data regarding sexual QoL [6].

Some studies [5,24,25] found that suicidal thought and suicide attempt rates were higher in people with DSD than in controls. Diamonds and Watson [27] found that secrecy, shame, and stigma caused the majority of difficulties in people with CAIS and that open diagnosis communication was still far from widespread.

Aims

The results on psychological adjustment in adulthood remain controversial and new research to obtain updated information is considered advisable in order to better understand the specific needs for care of women living with 46,XY DSD. We planned the study described below in order to assess clinical management, QoL, and the general psychosocial adjustment of individuals with 46,XY

DSD. As clinical management has changed in the past 10 years with shared decision making and more open diagnosis communication, in this study we wanted to see if the younger subjects, who experienced this change of clinical management, showed a better QoL and/or psychosocial well-being.

Methods

Participants and Recruitment Strategy

Because no national registry of all Italian 46,XY DSD adults is available, a selected sample was contacted. The sources of recruitment were both the pediatric endocrinological unit at the Bologna University Hospital and the adult members of AISIA. A total of 18 individuals under the care of S. Orsola Hospital were invited to participate. Of these, nine (50%) were accepted. In five (27%) cases, the letters, which were addressed to adults who had 46,XY DSD, were opened by parents who asked us not to continue to try to contact their daughters because they were getting on with their lives without knowing about their diagnoses. The remaining five (27%) recipients did not reply. As regards the other participants, a letter of invitation was sent to the 53 adult members of AISIA with 46,XY DSD, asking them to return their consent and the questionnaire by post; 34 persons (66%) agreed to participate in the study.

The total sample consisted of 43 adult females¹ with 46,XY DSD (60% of individuals contacted). The sample was formed mostly by XY females with any androgen action (CAIS, complete gonadal dysgenesis [GD] etc.) and in a small part by XY females with partial androgen action (partial androgen insensitivity syndrome [PAIS] and 5 α -reductase-2 deficiency).

Comparison Group

Comparison group consisted of 46,XX healthy women matched by age and educational level ($n = 43$; age, years: 34.5 ± 9.7 [range 22–51 years]), who had no historical or present medical conditions. The women included in the comparison group were recruited among medical, nursing, and welfare staff at the Paediatric Clinic of Bologna's

Sant'Orsola-Malpighi University Hospital and among students of medicine and obstetrics at Bologna University.

Consent

Written informed consent was obtained from each participant of both the 46,XY DSD group and the comparison group at enrolment in the study. The study was approved by the ethics committee for human investigations at the University of Bologna.

Main Outcome Measures

Taking into account the ethical issues involved in the research and the practical difficulties of collecting many different data, we planned a single and as brief as possible questionnaire, which included various instruments and some open questions, in order to investigate:

1. General indicators of psychosocial adjustment:
 - a) Educational background and employment situation
 - b) Sexual life milestones, partner relationships, and marital status
 - c) Living situation
2. Social behavior and withdrawal behavior (Achenbach and Rescorla's Adult Behavior Checklist [ABCL]) [28]
3. Psychological constructs:
 - a) World Health Organization Quality of Life Bref Italian version (WHOQOL-Bref) [29]
 - b) Depression and anxiety (ABCL)
4. We also asked the subjects to answer 17 open questions on many issues. In this article, we present their answers to questions about:
 - a. Sexual orientation: we asked them how they consider themselves among a multiple choice (heterosexual, homosexual, bisexual).
 - b. Psychological support

The full questionnaire is attached to the paper. The WHOQOL-Bref is a 24-item questionnaire and provides scores in four domains of perceived quality of life on a 0–100 scale: physical health, psychological health, social relationships, and environment.

ABCL provides a standardized description of behavior problems and competencies in adults. This questionnaire is broken down into cross-informant syndromes and Diagnostic and Statistical Manual of Mental Disorders-oriented scales. The cross-informant syndromes considered are: anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems (behavior of psychotic and obsessive spectrum),

¹"In this paper we will use the terms females or women in the meaning of persons with DSD assigned as female at birth and living in a female gender role."

attention problems, rule-breaking behavior, aggressive behavior. The six DSM-oriented scales are: affective problems, anxiety problems, somatic problems, attention deficit/hyperactivity problems, oppositional defiant problems, and conduct problems. This instrument generates a total problem score (TS), which is an index of psychopathological severity. Additional scores of maladjustment can also be estimated from the existing syndrome subscales and are computed on internalizing (IS) and externalizing (ES). ES includes impulsive behavior, conduct problems, and aggressive behavior. IS includes behaviors such as withdrawal, somatic complaints, anxiety and depressive Problems. The scores provided by the instruments are subdivided into three ranges: normal range scores (for all scales < 64, for TS, IS and ES < 60), borderline range scores (for all scales 65–69, for TS, IS and ES 60–63), and pathological range scores (for all scales ≥ 70, for TS, IS and ES ≥ 64). The Italian version of the questionnaire was translated in 2000.

The QoL study was carried out using the World Health Organization Quality of Life (WHOQOL) study. The Italian version [29] measures QoL in terms of four areas: physical, psychological, social, and environmental. WHOQOL score ranges from 0 to 100, with the higher values indicating a better QoL.

Statistical Analysis

All the data were anonymously collected in a database. Continuous data are presented as mean ± standard deviation, and categorical data are presented as count and percentage.

Psychosocial variables, QoL, and ABCL scales were assessed in the group of participants and in the comparison group. These data are presented using median and IQ range.

The results among the 46,XY DSD group will firstly be presented, then the data on the comparison group and the differences based on age and diagnosis will be given. As regards marital status, education, and work, the 46, XY DSD sample will be compared with the general Italian population data reported by the Italian Statistics Institute ISTAT (<http://dati.istat.it>) and EUROSTAT (<http://eurostat.it>).

Chi-squared test and Student's *t*-test or Mann-Whitney tests were used, as appropriate, for group comparisons. A *P* value of less than 0.05 has been considered statistically significant.

Results

The mean age of the 43 adult females with 46,XY DSD enrolled in this study was 31.5 ± 9.6 years (range 18–57 years). All subjects had 46,XY karyotype, and the majority (34/43, 79%) declared a diagnosis of CAIS. The other participants had various forms of 46, XY DSD (Table 1). Genetic diagnosis was available for 21 participants (Table 1). Three errors (14%) were recorded, comparing self-reported diagnosis with the genetic diagnosis performed in our laboratories. Thus, we estimated a 15% error in the 22 individuals for whom we have only the declared diagnosis. A median split at 29 years divided the sample into two similar subgroups: younger “subgroup 1” (≤29 years, *n* = 22, mean age 23.4 ± 3.7); older “subgroup 2” (>29 years, *n* = 21, mean age 39.9 ± 5.9) (Table 1).

Social, Work, and Educational Level

The majority of the women with 46,XY DSD (66.6%) were employed; 33% had a desk job, 41% of them were employed in cultural occupations (teacher, professionals). The remaining 33% of the

Table 1 Presumptive and genetically proven diagnosis in the two subgroups of the sample population (*n* = 43)

46,XY DSD Diagnosis*	Subgroup 1, <i>n</i> = 22 (age 23.4 ± 3.7 years)		Subgroup 2, <i>n</i> = 21 (age 39.9 ± 5.9 years)		Total, <i>n</i> = 43	
	Declared	Genetically proven (<i>n</i> = 11)	Declared	Genetically proven (<i>n</i> = 10)	Declared	Genetically proven (<i>n</i> = 21)
CAIS	18	4	16	7	34	11
PAIS	0	1*			0	1
Complete GD	1	1	0	1†	1	2
5α-reductase-2 deficiency	2	2	2	2	4	4
Leydig cell hypoplasia	1	1			1	1
SF1 haploinsufficiency	0	2*			0	2*
Unknown (non responders)			3	0	3	

*Three discordances on 21 diagnoses tested (between declared and genetically proven diagnosis)

†This case proven was one of the non responders

Table 2 Sexual orientation and respective diagnosis (corrected for the three errors revealed by genetic test)

46,XY DSD*	Sexual orientation		
	Heterosexual	Homosexual	Bisexual
CAIS	28		2
PAIS	1		
Gonadal dysgenesis	1		
5 α -reductase-2 deficiency	2	2	
Leydig hypoplasia	1		
SF1 def	1		1
Diagnosis unknown by the patient	1	1	
Total	35	3	3

*One person with CAIS and one person with gonadal dysgenesis did not responded to this question

sample was made up of students: 45% are studying for degrees in humanistic disciplines, 18% in psychological and social areas, 28% in law and economics, and only 9% in scientific subjects. The occupational level of our sample was higher than that of the 15- to 65-year-old Italian females (66% and 50%, respectively) (<http://eurostat.it>). Possession of a university degree was significantly higher in our sample than in the general Italian population (40% vs. 17%; $P = 0.003$) (<http://eurostat.it>).

Civil Status

About half of the women with 46,XY DSD (51%) lived with at least one parent, 21% lived alone or with housemates, and 28% had a new family (partner, husband), whereas the figure among Italian females aged 20–60 years was 56% ($P = 0.000$) (<http://dati.istat.it>).

Fourteen individuals were married or living with a partner; four women were separated or widowed, and 22 had never married nor lived with a partner. This information was missing for four participants. Four women were parents of adoptive children.

Gender Identity and Sexual Orientation

All individuals with 46,XY DSD in our sample feel they are comfortable in the female gender identity. Regarding sexual orientation, 35 women described themselves as heterosexual, two as homosexual, and three as bisexual (Table 2). Heterosexual orientation was higher but not significantly different in women with CAIS (93%) from those with other 46,XY DSD (63%). These data were missing for three persons. In the comparison group, all women answered that they were heterosexual, but it was not statistically different in the 46,XY DSD group ($P = 0.061$).

To a question of ABCL, 10 individuals, five from subgroup 1 and five from subgroup 2, reported they sometimes wanted to be of the opposite gender. One woman with complete GD (subgroup 2) declared she would often like to be of the opposite gender. The remaining 73% of the sample were satisfied with their gender. The answer was missing for one subject.

Age at Diagnosis and at Diagnosis Communication

Mean age at diagnosis was 11.6 ± 8.8 years in subgroup 1 and 14.8 ± 9.7 years in subgroup 2. Women in the younger subgroup discovered or were informed about their clinical condition significantly earlier than those of the elder group (mean age of 16.5 ± 4.2 vs. 21.2 ± 8.6 , respectively; $P = 0.048$).

Surgical Management

Thirty-two of 43 females (74%) underwent gonadectomy. In the women with CAIS, gonadectomy was performed on 27/30 (90%) at the mean age of 16.9 ± 9.7 years (range 0.5–36.0 years). Vaginal reconstruction was performed in three women (diagnoses: CAIS, $n = 1$, PAIS, $n = 1$, and 5 α -reductase-II deficiency, $n = 1$) at the ages of 10, 13, and 17 years. Clitoral surgery was performed on one female with PAIS when she was 13 years old, at the same time as vaginal reconstruction. Vaginal dilation was performed in a woman with 5 α -reductase-II deficiency when she was 24 years old.

Hormone Replacement Therapy

All participants who had gonads removed (32/32) were on hormone replacement therapy (HRT): the large majority (80%) received estrogens in various doses and formulations; thus, a detailed analysis of substitutive regimens employed by these women was difficult. Three women (20%) and two women (15%) in subgroups 1 and 2, respectively, received progestin, too. One woman with CAIS was on testosterone substitutive treatment. The HRT starting age was not significantly different between subgroups 1 and 2 (15.2 ± 3.5 years and 20.9 ± 9.1 years, respectively; $P = 0.074$).

Psychological Support

At diagnosis, psychological support was offered to 39% of the entire sample. Of these, 46% considered such support useful, whereas 19 individuals pursued psychological support in a private setting. Fifty-five percent of the women in the younger subgroup were offered psychological support at

Table 3 WHOQOL (median scores and IQ) range in the groups of patient and in the control group and in the two age subgroups of patients

	WHOQOL in 46,XY DSD and comparison group			WHOQOL in 46,XY age subgroups		
	Total 46,XY DSD Group median [25°–75°]	Comparison group median [25°–75°]	<i>P</i>	Subgroup 1 (≤29 years) Median [25°–75°]	Subgroup 2 (>29 years) Median [25°–75°]	<i>P</i>
Physical area	82.1 [71.4–92.9]	71.4 [64.3–82.1]	0.003	84.5 [75–96.4]	82.1 [71.4–89.3]	0.387
Environmental area	59.4 [53.1–68.8]	62.5 [53.1–68.7]	0.757	62.5 [53.6–68.8]	54.2 [45.8–62.5]	0.192
Psychological area	54.1 [45.9–62.5]	54.2 [50–58.3]	0.692	52 [50–62.5]	56.2 [53.1–62.5]	0.256
Social area	66.6 [41.7–75]	75.0 [58.3–83.3]	0.685	66.7 [41.7–83]	58.3 [33.3–66.7]	0.003

the moment of diagnosis communication, whereas only 47% of the older subgroup were ($P = 0.041$). There was a difference in the way individuals required psychological care: more often and earlier in the younger group than in the older one (70% vs. 35%, respectively; $P = 0.034$).

Regarding the use of psychiatric drugs, eight individuals did not respond to the question about whether they had had pharmacological therapy, whereas 11 persons declared they had (31.4%), and this percentage is higher than in the general Italian female population between 15 and 65 years (~12%) (D.R. Potente, Italian Survey 2010–2011, National Council of Research, pers. comm.)

QoL

The present sample of women with 46,XY DSD showed good QoL. Mean scores were over 50 in all four evaluated areas, although the score in the psychological area was the lowest one (Table 3). The most satisfying area was the physical one, with a median score of 82.1 ([1.4–92.9]) points, which was significantly higher than that of the comparison group ($P = 0.003$) (Table 3). No other significant differences between the study group and the comparison group were found (Table 3). The

younger subgroup showed significantly better QoL in the social area ($P = 0.003$) (Table 3).

ABCL Scales

The median and IQ scores of the eleven ABCL scales of persons with 46,XY DSD and women in the comparison group are summarized in Table 4. Persons with 46,XY DSD had a median score in the borderline range for IS and ES, which resulted significantly higher in the sample population than in the comparison group (Table 4).

The 46,XY DSD group showed median scores ≥ 60 in three subscales of ABCL (anxious and depressive problems, withdrawal behavior, and aggressive behavior).

Taking into account the individuals who had scores ≥ 65 (borderline for clinical relevance) [28], 42.9% of the sample resulted borderline for anxiety and depressive symptoms, 35% for withdrawal behavior, and 38% for aggressive behavior. The individuals with a total score of more than 63 (with a pathological significance) were 38% for IS and 31% for ES. Thirty-one percent of the sample had a score of >65 on the total problems scale.

Comparing the number of individuals with borderline scores in the 46,XY DSD group and in

Table 4 ABCL: median scores and interquartile range for the group of individuals with a 46,XY DSD and the comparison group. Percentage of borderline and clinical scores (considered as greater than 65). *P* values for comparison in percentages of borderline or clinical scores

ABCL scales	46,XY DSD group		Comparison group		<i>P</i>
	Median [25°–75°]	≥ 65 (%)	Median [25°–75°]	≥ 65 (%)	
Anxious and depressive symptoms	62 [54–60]	42.9	52 [50–56]	2.33	0.000
Withdrawal behavior	62 [51–65]	35.7%	51 [50–53]	6.98%	0.001
Somatic complaint	57 [51–65]	26.19%	54 [01–60]	11.63%	0.086
Thought problems	58 [51–62]	23.81%	51 [50–54]	2.33%	0.003
Attention problems	58 [52–65]	28.57%	56 [50–59]	9.30%	0.023
Aggressive behavior	62.5 [58–67]	38.1%	52 [51–55]	6.98%	0.001
Rule breaking behavior	52 [51–59]	14.3%	51 [50–55]	9.3%	0.476
Intrusive behavior	57 [51–65]	30.9%	51 [50–56]	4.6%	0.001
Internalizing (IS)	63 [53–69]	38.1%	52 [43–57]	4.6%	0.000
Externalizing (ES)	60 [56–66]	31%	48 [47–55]	4.6%	0.000
Total problems	60 [52–65]	31%	51 [44–53]	2.3%	0.000

Table 5 Comparison between 46,XY DSD age subgroups in the ABCL scales

ABCL scales	Subgroup 1 (≤ 29 years) Median [25°–75°]	Subgroup 2 (> 29 years) Median [25°–75°]	<i>P</i>
Anxious and depressive symptoms	58.5 [53–65]	66.5 [59–72]	0.032
Withdrawal behavior	55 [50–65]	62 [53–68.5]	0.077
Somatic complaints	54 [51–58]	60.5 [54–66]	0.017
Thought problems	51 [51–58]	58 [56.5–68]	0.017
Attention problems	57.5 [51–63]	60 [52.5–65.5]	0.586
Aggressive behavior	60 [53–63]	66 [62–68.5]	0.004
Rule breaking behavior	51.5 [51–58]	53.5 [51–63]	0.357
Intrusive behavior	55.5 [51–61]	62.5 [52–65]	0.127
Internalizing (IS)	58.5 [53–63]	67 [58.5–72]	0.029
Externalizing (ES)	57.5 [53–62]	62 [59–70.5]	0.018
Total problems	57.5 [49–62]	65 [58–68]	0.008

the comparison group, a significant difference was found in all but one (rule breaking behavior) the scales (Table 4).

As regards the age, the younger 46,XY DSD subgroup showed better adjustment: they showed less ES and IS, lower levels of anxiety and depression, and fewer thought problems, somatic complaints, and aggressive behavior (Table 5).

Suicidal Tendency and Thoughts

Three individuals with 46,XY DSD declared they thought about suicide sometimes; only one person declared she often and deliberately try to harm or kill herself; three individuals declared they sometimes tried to harm themselves. These results did not show a significantly higher suicidal tendency than the comparison group, in which four persons responding to the question about whether they tried to harm themselves or thought about suicide chose the answer “sometimes”; one individual chose the answer “often.”

Differences Between Women with CAIS and Other 46,XY DSD

No significant differences in QoL and in psychological variables between women with CAIS and those with other 46,XY DSD were found (Tables 6 and 7), but the small number of people in the latter group might have influenced these results.

Discussion

This study suggests that the presence of 46,XY DSD seems to have an influence on educational,

socioeconomic, and relational areas. This sample of women with 46,XY DSD achieved a higher educational level and were more engaged in work compared to the age-matched general Italian female population, whereas a lower percentage of females living with 46,XY DSD were married or in a stable relationship. Thus, a higher percentage lived with at least one parent in adulthood.

As previously reported [9,19–22], the perceived QoL was good, and the present sample showed no significant differences from the comparison group, suggesting that 46,XY DSD permits a satisfactory long-term outcome. A challenging point was the significantly better scores in the physical area, despite the necessity for long-term follow-up in a clinical setting, HRT, and some medical and social worries. This finding may indicate that people with 46,XY DSD feel they are better followed and medically protected. Because scores in marital, relational, and parental areas were lower than in the comparison group in this and in other studies [10,20,30,31], the attention to body and bodily activity may also represent emotional compensation. The decrease in psychological distress in the younger subgroup may be related to changes in medical management and to a wider offer of psychological care, as well as to the action of Users' Associations and Support Groups, but this issue needs further investigation.

Female sexual identity and sexual orientation toward male was predominant in this sample (85%), with no differences between the two sub-

Table 6 WHOQOL: Comparison between (median scores and IQ) range in the subgroups of women with CAIS and other 46,XY DSD

WHOQOL scales	CAIS Median [25°–75°]	Other 46,XY DSD Median [25°–75°]	<i>P</i>
Physical area	82.1 [75–92.9]	82.7 [71.4–98.2]	0.716
Environmental area	62.5 [56.2–68.8]	53.3 [43.8–62.5]	0.131
Psychological area	50 [45.8–62.5]	56.2 [50–62.5]	0.338
Social area	66.6 [41.7–75]	66.6 [37.5–79]	0.654

Table 7 ABCL scales: Comparison between (median scores and IQ) range in the subgroups of women with CAIS and other 46,XY DSD

ABCL scales	Subgroup 1 (CAIS) Median [25°–75°]	Subgroup 2 (Other 46,XY DSD) Median [25°–75°]	P
Anxious and depressive symptoms	62.5 [58–67]	58 [51–72]	0.565
Withdrawal behavior	57 [51–65]	62 [51–67]	0.388
Somatic complaints	57 [54–65]	52 [50–62]	0.267
Thought problems	58 [51–62]	58 [51–68]	0.493
Attention problems	59 [53–66]	56 [50–64]	0.261
Aggressive behavior	62 [54–68]	63 [60–65]	0.734
Rule breaking behavior	51.5 [51–69]	51 [51–58]	0.316
Intrusive behavior	56.5 [51–65]	61 [53–65]	0.414
Internalizing (IS)	63 [54–68]	57 [52–71]	0.723
Externalizing (ES)	59.5 [56–67]	60 [57–63]	0.825
Total problems	60 [52–65]	57 [54–68]	0.882

groups. This is not surprising, as the majority of the individuals in the cohort had a diagnosis of CAIS (93% heterosexuals), as in this condition there are no androgen actions on the brain. In Leydig cell aplasia and in complete GD, severe impairment of testosterone secretion is also present from early intrauterine life [1]. In the women with different diagnoses (PAIS, GD, and 5 α RD-), a high percentage of heterosexual and bisexual individuals was present (44.4%), but significance was not reached probably related to the small sample. The higher percentage of homosexual and bisexual orientation in the latter group is possibly related to the prenatal and postnatal exposure of the central nervous system to sex steroid action and to sociocultural influences during childhood possibly related to higher masculinization at birth [32,33]. As regards the homogeneous heterosexual orientation declared by our comparison group, we wonder if this reflects a persisting embarrassment about disclosing anonymously this aspect of personal behavioral profile.

For the psychological and behavioral aspects analyzed by ABCL, as already reported [24,25], we found that the individuals with 46,XY DSD showed borderline median scores for IS and ES. In agreement with other studies [19,20], they were also more likely to be depressed and anxious, showed more withdrawal and aggressive behavior, and had more thought and attention problems than the women in the comparison group. Assessed together, these data suggest that persons with 46,XY DSD may have higher psychological distress than the general female population. In addition, this sample expressed lower score rates in psychological areas than in the other QoL areas. Our data confirm that in the younger group, there was a sensible lower age of diagnosis communica-

tion confirming the results of Liao et al. [11]. Because the younger subgroup showed better psychological adjustment, changes in DSD clinical management seem to improve quality of care, allowing for a better long-term outcome through a new sensitivity and awareness in medical staff and increased availability of psychological support [34]. Psychological support is often seen as an individual technical treatment provided by specialists. As people with DSD are often not sick people according to the traditional disease-centered perception, psychological support should be regarded as the capacity of the multiprofessional team to offer a clear understanding of the different conditions in order to involve them and family members in the decision-making process and in all the life-long needs of medical care.

Finally, these data indicate that medical approaches should be improved and more evidence based. For example, HRT in this sample was very variable and likely to be based on the physician's personal experience with postmenopausal women instead of young adults. Although no evidence-based data on better hormone formulations, routes of administration, doses, and monitoring parameters are available to guide clinical practice for people living with DSD, recent data and the availability of new formulations may lead to a more physiological approach for young adults instead of the empirical treatments largely used in the past. This could lead to more homogeneous protocols regarding therapy and specific age-related doses, avoiding the use of progestins in women without a uterus [35]. Such complex objectives can only be achieved through individually tailored HRT, long-term monitoring and, where possible, management in conjunction with tertiary centers that have documented experience in this field.

The major limit of this study was the relatively small sample size and the even smaller subgroups for statistical analysis. In addition, 2/3 of the participants were CAIS, and the majority were volunteers from a support group, representing a selected sample. This approach raises some problems in terms of generalizing our findings for the entire population of females with 46,XY DSD. Although some people think that dissatisfaction and worse outcomes might push people to join support groups, our experience suggests that worse outcomes are more likely to be linked to a secretive and isolated status. Finally, unconfirmed self-reported diagnosis in about half the sample represents another weakness. Nevertheless, we would like to underline that the sample group of this study is one of the largest in 46, XY DSD literature.

Conclusion

Our data support the conclusion that psychological distress is one of the chief negative outcomes of DSD management. The capacity of healthcare staff to address the health needs of children, adolescents, and adults with 46,XY DSD properly and to interact in an open way by speaking clearly to parents right from the moment of diagnosis communication onward may improve the long-term outcome, leading to less need for specialized individual interventions. Special attention should be paid for people who underwent genital surgery, as these persons may experience higher problems with sexual functioning [26]. Increased action of patients' associations and support groups may be an additional key factor in proposing an approach more based on patient's emotional needs. These associations offer the possibility for people who have lived in an isolated dimension for a long time to meet people with the same conditions and discuss any aspect of the experience of living with a DSD. This empowers individuals to make decision about their own health and helps overcome the experience of secrecy and loneliness.

Further studies will show whether the improvement in DSD care and the tackling of connected psychological and social factors will change the result of current research that shows that people living with 46,XY DSD are less satisfied with their social lives than comparison subjects.

We recommend that all adults and children with 46,XY DSD and their parents should be offered psychological support and counseling. Instead of the traditional models of individual psychological

care, we would suggest group therapy, collaboration with support groups, working with groups of parents, and encouraging the multiprofessional team to adopt a more sensitive approach that gives more space to the psychological sphere.

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Conflict of Interest: The author(s) report no conflicts of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1 The AISIA Survey Questionnaire.