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Mental Health Status Of Individuals With Sexual Development Disorders: A Review

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Abstract

Health care recommendations for people with Disorders of Sex Development (DSD) include mental health attention and active participation of psychiatrists and psychologists in dedicated multidisciplinary teams. Thereby, it seems crucial for them to improve knowledges about specific difficulties and needs of these patients. The aim of this paper is to report in a synthesising manner the recent works evaluating the mental health and psychological status of individuals with DSD. After research conducted using PUBMED and SCIENCEDIRECT, 18 studies were inventoried and qualitatively analyzed in response to three main questions: do individuals with DSD suffer more frequently and/or more severely from psychological conditions or mental disorders? From what kind of disorder do they suffer? What are the determinant factors involved in their development? Our work highlights an increased risk of affective disorders in individuals with DSD, particularly anxiety and depressive disorders and interpersonal difficulties. Studies identified some potentially determining factors implicated in their development, among which the etiology of DSD, the life stage, the age at the time of diagnosis, and the lack of conformity of sexual phenotype with sex assignment. Taken together, the etiology of DSD, the lack of conformity of sexual phenotype with sex assignment and the feeling of being different from peers **seem to be interesting factors to study in the future**. Multicentric and longitudinal studies using standardized evaluation and control groups should be the most robust way to improve knowledge about these preoccupations.

Key words :

Disorder of sexual development, psychology, psychiatry, affective disorders, mental health

Introduction

The term *Disorders of Sexual Development* (DSD) refers to a complex and heterogeneous nosographic entity defined as “congenital conditions in which development of chromosomal, gonadal or anatomical sex is atypical” ; it involves multidisciplinary support including specified members working in the field of mental health care[1]. In the actual literature, studies highlighting the mental impact of the condition are scarce [2]. The aim of this work is to synthesize the data currently available in this field.

Materials and Method

The PUBMED and SCIENCEDIRECT databases were used together using the following search term combinations : “DSD AND psychiatry” and “DSD AND psychology”. In addition, bibliographies of selected articles were examined and studies with the same criteria, published between 2006 and 2016 , were included. The only studies selected were those targeting DSD populations where the principal judgment criteria was mental health evaluation. We did not include studies evaluating non-pathological symptoms or traits (**like impulsivity studied in isolation or autistic traits that don’t reach a clinical cutoff, features that not predjudge of fonctionnal consequences**), studies specifically evaluating gender identity or cognitive function, or studies exclusively targeting sex chromosome abnormalities. Furthermore, we did not include purely qualitative studies, life experiences, and case reports. Finally, selected articles were completely and rigorously assessed by one rater **in a free manner and without systematic tool**. Then, based on the qualitative aspect of the datas, the review was organized around three questions: (1) Do individuals with DSD suffer more frequently and/or more severely from psychic troubles or mental disorders ? (2)

From what kind of affective troubles/mental disorders do they suffer ? (3) What are the determinant factors involved in their development ?

Results

721 studies were obtained as a result of the algorithms. Among these, 146 studies were indeed about DSD. After filtering by inclusion and exclusion criteria, 18 studies were selected and categorised according to the nature of the population studied. Among the 18 individual samples, 10 were composed of individuals with heterogenic etiologies of DSD, 4 were exclusively composed of women with Congenital Adrenal Hyperplasia (CAH) and 4 were composed of women suffering from various malformative etiologies (3 were about the Rokitansky-Mayer-Küster-Hauser Syndrome or MRKHS and 1 was about vaginal agenesis). We summarized methodologies and principal results of each study in **Tables 1, 2, and 3**. One study was not totally available, so the data was extracted from the authors' abstract. **A notable methodological heterogeneity between the 18 studies prevented a quantitative analysis of results.**

1) Do individuals with DSD suffer more frequently and/or more severely from psychological troubles or mental disorders ?

Only 2 of the 18 studies resulted in no increase of psychic disorders in their samples [3,4]. Results of the 16 other studies showed an increased amount of psychic disorders either evaluated in terms of mean score or in pourcentage of clinical cases. **Schützmann et al. (2009)** showed that the mean BSI score (Brief Symptom Inventory) for the DSD sample was

equal to the mean BSI score of control populations suffering from renal insufficiency and did not exceed that of control populations suffering from HIV, nor that of a control group composed of non-treated out-patients suffering from anxiety. Also, 59 % of the sample was considered as clinical cases (against 63,3% in the sub-group of patients with HIV). In the same study, the suicidal thoughts prevalence was higher than that of a control sub-group composed of women without any history of trauma, but was lower of that of the subgroup of women with a history of physical and sexual trauma [2]. **Krupp et al. (2014)** showed no increase in the mean score of Global Severity Index (GSI), whereas the number of clinical cases (defined as an ISG T-score higher than 63 or a T-score higher than 63 in two or more subscales) was increased. **Johannsen et al. (2006)** reported an increase of seeking health care for severe psychological conditions, whereas no increase for average psychological conditions (categories are not specifically defined by authors according to the motive and duration of the follow-up) [5]. In addition, some authors found an increased prevalence of psychiatric diagnoses in their DSD samples : **Hsin-Yi Lang et al. found an high pourcentage of axe 1 diagnosis of DSM-V (Diagnostic and Statistical Manual of Mental Disorders), 36,5% in their sample, comparing to 14,8%-22,7% in general population ; Engberg et al. found 2 times more diagnosis all mixed in their sample comparing to general population ; Burcu et al. made a psychiatric diagnosis among 25% of their sample [6–8].**

Regarding the suicidal risk, 5 studies have evaluated it by screening the history of suicidal thoughts or the number of suicide attempts [2,5,8–10]. Among them, 3 showed an increased suicidal risk in their DSD sample : **Johannsen et al. found a significant higher rate of previous suicidal thoughts in their patient group compared to healthy control (37,7% and 12,9% respectively, $p < 0,05$) and a no significant higher rate of suicide attempt in their patient group compared to healthy control (11,6% and 4,3% respectively, $p > 0,05$) ;**

Schutzmann et al. (2009) found a significant higher rate of self-harming behavior in their DSD sample comparing to a non traumatized comparison group (women without any history of sexual or physical abuse) (13,5% of self-harming behaviour in the DSD sample against 3,5% in the non-traumatized women, $p = 0,01$) ; also, they found that the rate of previous suicidal thought was significantly 2 times higher in the DSD sample comparing to the non traumatized comparison group (respectively 46% and 20%, $p=0,01$) ; on the other hand, the rate of previous suicidal thought was significantly higher in the sample of women with both sexual and physical abuse compared to DSD sample (respectively 71% and 46%, $p=0,01$); Krupp et al. found a higher rate of suicidal attempt in their DSD sample (18% in their CAIS sample and 8% in their MRKHS sample) compared to the prevalence found in a german non-clinical comparison sample (lifetime suicide attempts : 1,7% ; 95% CI 1,24 – 2,16) [2,5,9].

2) From what kind of affective troubles/mental disorders do individuals with DSD suffer ?

Globally, the most represented symptoms in DSD samples were anxiety in its wider definition and also in its adaptive aspects [5,11–14], along with symptoms of depression [2,6,7,9]. Additionally, we found difficulties in interpersonal areas, including interpersonal sensitivity, withdrawal, and social anxiety [2,6,15].

3) What are the determinant factors involved in their development?

DSD etiology

Congenital Adrenal Hyperplasia (CAH)

The 4 studies exclusively evaluating CAH (amounting to a total of 427 patients) found an increased level of psychic troubles in their samples [6,8,11,12]. These originate mostly from

anxiety disorders (generalized anxiety, adjustment disorders, social anxiety) and depressive disorders (dysthymic disorders, major depressive disorders). Concerning studies in which a sub-group of women with CAH were individualized, **Schützmann et al (2009)** found that women with CAH (n=11) have comparable percentage of clinical case than other sub-groups whereas their mean BSI-score were significantly lesser [2] while **Johannsen et al. (2006)** found that the CAH sub-group has the highest levels of psychological distress when compared with the rest of the samples (n=40) [5]. Regarding the implication of the HPA (Hypothalamic-pituitary-Adrenal) axis in stress, it has been suggested that CAH could induce increased response to stress and in this way contributes to anxiety disorder susceptibility. Thus, **Charmandari et al. (2004)** reported a chronic and moderate hypocortisolism in relation to individuals with CAH, which leads to an increased compensatory secretion of CRH (Corticotropin-Relasing Hormone), suspected to be implicated in anxiety and depressive disorder susceptibility [16]. Furthermore, **Falhammart et al. (2014)**, in their study of men with CAH (and not affected with DSD) found a global increase of psychiatric diagnoses including personality disorders, alcohol abuse, and suicidality [17]. These results echo with those from **Engberg et al. (2015)** who reported a notable increase of substance and alcohol abuse in women with CAH [8]. Authors hypothesise that dysregulation of the HPA axis could increase the risk of addictions. On the other hand, alcohol consumption can be considered as a pathological attempt to self-medicate anxiety symptoms in line with DSD. For example, **Hsin-Yi-Liang et al. (2008)** raise the issue that masculine secondary sexual characteristic appearances in women with CAH are events which are possibly the source of adjustment disorders [6].

Concerning the different sub-types of CAH, 3 studies highlighted that the salt wasting form was associated with more severe psychic troubles [2,6,8]. This is in line with the intrinsic

severity of the pathology which requires more intensive care and is associated with a higher morbidity and mortality.

Complete Androgen Insensitivity Syndromes (CAI)

Complete Androgen Insensitivity doesn't seem to increase the risk of psychologic distress among all other etiologies and appears equal to the other sub-groups in the 3 studies identifying it [2,9,10]. Solely, **Johannsen et al. (2006)** reported a decreased psychological distress and suicidality in this group compared to others : **there were 10% of previous suicidal thoughts and no previous suicidal attempt in this subgroup against 12,9% and 4,3% respectively in the healthy control (p>0,05). Also the total score on the Hopkin Symptom Checklist (psychiatric scale evaluating depression, anxiety and somatization) was 1,9 in the CAIS subgroup, against 2,9 in the healthy control (p>0,05) [5].** However, analysing these results requires caution given the small sample size.

Malformative etiologies of DSD

All 5 studies targeting individuals with malformative etiologies of DSD (vaginal agenesis and MRKHS) reported moderate psychological impact in their sample [9,13,14,18,19]. In contradiction with authors suggesting that psychological impairments do not subsist after the critical period of diagnosis [20], two studies found increased levels of psychological distress even after the diagnosis procedure and for however long after this period [9,14]. However, the timing of diagnosis seems to specifically contribute to the increased risk of developing negative feelings, intense reactions, or acute psychological conditions [13,18].

Some authors suggest that age is not a linear correlation factor in the evolution of psychological distress. They rather support the idea that conditions are silenced or increased by other variables which are more or less actualized depending on life stages (and related to intimate relationships, sexuality, or fertility) [9].

Life stages

Two studies outline that older individuals were more affected by psychological distress than younger ones [2,8]. However, the two studies exclusively composed of children found an increased level of psychological distress rather characterized by externalized conditions such as behavioral problems, aggressivity or ADHD (Attention Deficit and Hyperactivity Disorder) [7,15]. Surprisingly, the two studies targeting adolescent samples did not find any increase of psychological distress compared with the data obtained from the controls [3,15]. This appears in contrast with clinical intuition, whereby the individuation procedure of adolescence and its close relationship with peer identification involving the sensibility towards the pressure of normality or conformity [3]. However, and this being an argument of **Kleinemeier et al. (2010)**, major challenges of DSD (being engaged in a durable relationship, desiring a child) are not salient at the adolescence period and are more actualized at adulthood [3].

Age of diagnosis

Concerning the age at which a diagnosis is made, results are conflicting. Some studies find that late stage diagnosis is associated with better psychological outcomes, suggesting that a

well stabilised identity and personality constructed before diagnosis can act as a protective factor against self and existential reconsiderations [9,13,21]. Others suggest the opposite whereby late stage diagnosis could be deleterious and associated with increased psychological distress [6,15]. It is important to note that these two studies were carried out in nations where access to care is limited (Taiwan, Indonesia). In European countries, the age at which the diagnosis was made is in reality correlated to the nature of the etiology itself. Those with late stage diagnosis and better outcomes were specifically asymptomatic before the adolescence period and could not be diagnosed earlier. On the contrary, some etiologies required an early diagnosis and the lack of one could lead to serious complications (particularly CAH).

Lack of conformity of sexual phenotypes with sex assignment

The lack of conformity of sexual phenotypes with sex assignment (including atypical genitalia) seems to be a significant factor for the development of psychic morbidities in DSD individuals. Indeed, among the 3 studies interrogating this aspect [2,5,22], one found a positive correlation between degree of virilization at time of diagnosis and depression and anxiety scores and also with previous suicidal thoughts [5]. Another found a significant increase of emotional and behavioral problems in the sub-group of women with atypical genitalia compared with the sub-group not affected by this condition [22]. As noted by **Johansen et al. (2006)**, these results could be explained as a consequence of a complex and disruptive assignment at birth with extensive and stressful investigations for diagnosis procedures and sometimes the need for intensive medical treatment. This could also be considered as a gender identity challenge. As a consequence, these results suggest the

contribution of the “abnormal aspect” of this trait towards stigmatization and a source of psychological distress [3,9]. Also, **Kleinemeier et al. (2010)**, found a significant higher rate of interpersonal difficulties when the puberty have to be artificially induced [3].

Limits to the data analyses

Lack of internal validity

The principal limitation of the studies included in this review is the small size of the DSD samples. Among 18 studies, only three have included more than one hundred patients whereas 5 of them concerned less than 25 individuals. Some etiologies were therefore clearly under-represented, particularly gonadal dysgenesis and androgen synthesis or action abnormalities, which are often regrouped in a sample called “XY, DDS”. Furthermore, we observed an over-representation **of individual assigned as** women (1048 women in total, against 58 men, data not shown in two studies) [7,15]. Additionally, all studies are cross-sectional and do not allow the demonstration of causal effects. Concerning the recruitment procedure, 13 studies had recruited their samples from hospitals [4–7,10,12–15,18,19,21,22], 3 studies had recruited their samples in hospital and through support groups, meeting and conferences [2,3,9], and 1 used national diagnostic registers [8]. For 1 study, this information was not provided [11]. Each of these recruitment procedures could lead to various selectivity biases. Furthermore, among the 18 studies, half of them did not specifically constitute a control group in the study design but used the data available in the literature. This suggests a questionable comparability often discussed by authors. Some are purely descriptive and do not compare their results with any others [7,18,21]. It can be raised that none of the studies have explored other risk factors for psychological distress

such as family history of psychiatric conditions and/or stressful life events others than the DSD condition. Only 1 study evaluates the existence of stressful life events with a standardized tool (the Stressful Life Events Schedule), using this variable as a correlation factor in statistical analyses [13].

Lack of external coherence

Although our results appear less heterogenous than those of **Schützmann et al. (2007)**, several numbers of limitations restrict group comparability between studies. Also, because of the cross-sectional aspect of all studies, samples may be influenced by several confusion factors (life stages and steps taken towards care for example). In addition, the heterogeneity of recruitment procedures (hospital vs support groups) and the characterization of the samples (age, etiological sub-group delimitations) represent further limitations towards study comparisons. Moreover, the judgment criteria were different between studies. Some used generalised screening tools used in mental health whereas others identified diagnoses by semi-structured or structured interviews. Finally, control groups were not comparable between the different studies (**cf Tables 2, 3 and 4**).

Limitation, discussion and perspectives

It is important to higligh the limits of this work. First, the chosen methodology has created a selection bias in the studies inclusion. We don't have access of studies published before 2006 even if we can rely on the review of Schützmann et al. Also, the heterogeneity of the studies included did not permit a quantitative analyse of the data and we could just

extracted the majoritary tendency of the datas. Thus, this work can be qualified as a narrative review and doesn't have the robustness of a systematic review. In the same way, datas don't permit the use of validated tools for their analyse and give the possibility to a subjective bias in their extraction.

However, this work highlight **a tendency of Individuals with DSD to be** more vulnerable and more affected by psychological conditions. These conditions seem to be in the area of anxiety and depressive disorders and interpersonal difficulties. **Also, we found a tendency of individual with DSD to have an increase risk of suicidal thoughts and attempts.** The results of the different studies are too scarce and inconsistent regarding the potentially determining factor which could be identified in the development of such conditions (etiologies of DSD, life stages, age at the time of diagnosis and lack of conformity of sexual phenotypes with sex assignment). We can only note tendencies that need further robust studies. Thus, the lack of conformity of sexual phenotypes with sex assignment viewed trough 3 presentations **(physical virilization in person assigned in the women sex, existence of atypical genitalia, and needing to be engaged artificialy in puberty) seems to be relevant in the development of psychological distress in individuals with DSD and should be an interesting factor to study in the future.**

Overall, we can mention the positive evolution across time regarding the quantity and the quality of studies in this field. The review published by **Schützmann et al.** 10 years ago highlighted the extreme paucity of knowledge regarding the mental health and psychological status of individuals with DSD (11 studies between 1956 and 2005) and about methodologies, already attested about the limitations of small sample sizes, non-standardized data and recruitment procedures exclusively centered in hospitals. Authors

concluded at this time that “any collection of new samples based on a different mix of DSD syndromes, treatment histories, sampling sources, and self-selection biases will produce a different pattern of results” [2]. Actually, although the literature remains scarce, there are more studies and their methodologies have improved. We can see multicentric recruitment, including other partners than hospitals such as support groups, and the majority of evaluations carried out by standardized measures. Also, sample sizes are larger. Finally, the psychological field of individuals with DSD, which constitutes a rare, complex and heterogeneous condition and also raises sensible questions in the ethics and social field, seems to be a real challenge for scientific researchers. In this area, the gold standard should be represented by a multicentric, longitudinal, standardized and controlled study.

Declaration of interest

No interest to declare.

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Table 1: Methodologies and principal results from studies evaluating heterogenic DSD samples

Reference	Recruitment and participation rate (PR)	DSD sample	Control group	Main criterion and evaluation	Results
Johannsen et al. (2006) Denmark	Hospital Patients diagnosed between 1953 and 2003 PR : 81%	N = 70 women CAIS (n = 11, median age = 35,4 years) « virilized 46, XY and 46, XX women » (n = 16, median age 39 years) GD (n = 3, median age 29,6 years), CAH (n = 40, median age 0,3 years)	« operated controls » (isolated genital malformations) (n = 6) « matched controls » (n = 70)	Structured interview : history of contact to psychologist, psychiatrist and psychiatric departments, previous suicidal thoughts or suicidal attempts, present psychopharmacological treatment Self-reported scale (mental distress) : Hopkins Symptom Checklist SCL-90-R (missing data for 9 patients)	Higher frequency of counseling due to severe symptoms (p=0,06) Suicidal thoughts significantly more frequent (p=0,002) Tendency to have more psychopharmacological medication (p=0,08) Anxiety score significantly higher at the SCL-90-R
Schützmann et al. (2007), Germany	Hospital, support groups, internet TR no measurable 16 patients recruited by their doctor, 12 by support groups, 9 by the internet	N = 37 patients (34 women, 3 men) Mean age 30.5 years (16-60 years) 17β-HSD (n=2), 5α-RD (n=3) CAIS (n=5), PAIS (n=6), GD (n=10), CAH-SV (n=3), CAHS-SW (n=8)	Reference group (n = 300) “HIV “ group « chronic kidney insufficiency » group « outpatient psychotherapy patients with anxiety disorders » group 4 sub-groups of women with history of traumatism (no trauma, sexual abuse, physical abuse, and sexual and physical abuse)	Self-reports : BSI (Brief Symptom Inventory) Self-Harming, Behavior, Suicidal Thoughts, and Suicide Attempts : qualitative questions	Increased levels of psychic troubles, equally to « chronic kidney insufficiency » and « outpatient psychotherapy patients with anxiety disorders groups and lower than « HIV » group Increased of Self-Harming, Behavior, Suicidal Thoughts, and Suicide Attempts equally than “physical abuse” or “sexual abuse” groups

K.Gueniche et al. (2008), France	Hospital PR : 38,5%	N = 15 women Age 18-41 years XY, DSD (N=15), GD, androgen action or synthesis anomalies (no sub-group)	No control group	Semi-directive interview with qualitative analysis	Psychological distress qualitatively increased according to authors
Kleinemeier et al. (2010), Germany	Hospital, support groups, conferences, internet Multicentric (4 centers in Germany, 5 in Austria and Switzerland) between 2005 et 2007 PR : 75%	N = 60 patients (54 girls, 6 boys) Mean age 14,5 years (13-16 years) DSD, XX, P-F (n = 29) ; DSD, ; XY C-F (n = 7) ; DSD, XY, P-F (n = 18) ; DSD, XY, P-M (n = 6) P : androgen partial effects, C : no androgen effect M : rearing in male gender, F : rearing in female gender	Control group (N = 546)	Self-reports : Mental Health : SDQ (Strengths and Difficulties Questionnaire)	No increase of psychological distress
Fagerholm et al. (2011), Finland	Hospital Patients with feminizing genitoplasty between 1980 et 2008 (retrospective datas) PR : 53%	N = 24 women Median age 25 years (15,5-36,7 years) 46, XX CAH-SW (n = 12) ; 46, XX CAH-SV (n = 3) ; 46, XX maternal virilization tumor (n = 1) ; 46, XY CAIS (n = 3) ; 46, XY PAIS (n = 5)	2 comparative groups Schützmann and al. group and population based control group	Self-reports : SCL-90 Qualitative evaluation : opinion about operation temporality and chirurgical intervention memories	No increase of psychological distress
Burcu et al.	Hospital	N = 51	No control group	Semi-structured interview : K-	Psychiatric diagnosis identified in

(2013), Turkey		Mean age 7,83 years (1-18 years)		SADS (DSM-IV) : Kiddie-Schedule for Affective Disorders and Schizophrenia	13 individuals (25%)
Krupp et al. (2014), Germany	Hospital, support groups, internet	N = 61 women MRKHS (n = 50, mean age = 23,7 years) SICA (n = 11, mean age = 38,7 years)	General population datas	Self-reports : BSI and PHQ-D (Patient Health Questionary) History of suicidal attempt	GSI (Global severity Index) mean) under the cut-off for clinical case High frequency of clinical cases (54,5% for CAIS and 55,1% for MRKHS) History of suicidal attempt significantly higher
Franco d'Alberton et al. (2015), Italy	Hospital PR = 50% AISIA (Italian Androgen Insensitivity Syndrome support group) PR : 66%	N = 43 women Mean age 31,5 +/- 9,6 years 46, XY DSD (CAIS, n=30, PAIS, n=1, GD, n=1, 5 α -RD, n=4, Leydig hypoplasia, n=1, SF1 def, n=2, diagnosis unknown n=2, no response for 2 patients) 2 sub-groups : \geq and \leq 29 years	Healthy control group (n = 43 women)	Self(reports : Anxiety-depression and social behavior : ABCL (Achenbach and Rescorla's Adult Behavior Checklist) History of psychological support or suicidal though or attempts	Clinical case frequencies : 31% for Externalizing troubles, 38% for Internalizing troubles No significantly higher suicidal tendency
Ediati et al. (2015), Indonesia	Hospital Between march 2007 and may 2011 PR : 70,2%	N = 118 Age 6-41 years (60 children, 24 adolescents, 34 adults) 46 XX/XY (n=6), AIS (n=16), 46, XY GD (n=28), 46, XY « hypomaskulinized » (n=41), CAH(n=24), cloacal malformation	Matched controled group (n=118)	Self-reports : Emotional and behavioral problems : ASEBA Scales (Achenbach System of Empirically Based Assessment) Children : CBCL 6-18 (Child Behavioral Checklist, parent-report measure)	Significantly higher total problems on parent reports for children Significantly higher score at anxious/depressed scale in adult sample No increase of psychological distress in adolescent sample Significantly higher distress in

		(n=2)		Adolescents : YSR (Youth-Self-Report) Adults : ASR (Adult-Self-Report)	adult sample than in children and adolescent samples
Nita G.M de Neve-Ethoven et al. (2016), The Netherlands	Hospital Multicentric Between 2007 and 2012 PR : 50%	N = 120 3 sub-groups : 46, XY FG Women (n=35), median age 24 years 46, XY AG et 46, XX AG Women (n=69) Median age 27 years 46, XY AG et 46, XX AG men (n=16), median age 25 years FG : female genitalia, AG : atypical genitalia	Dutch patient group reference data (patients suffer from fibromyalgia, n=372)	Self-reports : Experienced fatigue : CIS8R (Checklist Individual Strength-Subjective Fatigue scale) Emotional and behavioral functioning : ASR (Adult Self Report) Measure on self-esteem : RSES (Rosenberg Self-Esteem Scale)	No increase of psychological distress in the total sample Significantly more emotional and behavioral problems in women born with atypical genitalia

CAIS : Complete Androgen Insensitivity ; PAIS : Partial Androgen Insensitivity ; 5 α -RD : 5-alpha reductase deficiency ; 17 β -HSD : 17-Béta-hydroxysteroid dehydrogenase deficiency ; GD : gonadal dysgenesis ; CAH-SV : Congenital Adrenal Hyperplasia Simple-Virilizer ; CAH-SW : CAH with Salt Wasting syndrome

Table 2 : Methodologies and principal results from studies evaluating women suffered from Congenital Adrenal Hyperplasia

Reference	Recruitment and participation rate (PR)	DSD sample	Control group	Main criterion and evaluation	Results
Hsin-Yi-Liang et al. (2008), Taiwan	Hospital PR : 64%	N = 11 women Mean age 15,3 +/- 5,6 years (8–25 years) CAH (N = 11)	No control group	Semi-structured interviews : K-SADS-E (Kiddie Schedule for Affective Disorders and Schizophrenia) DSM-IV (Diagnostic and statistical Manual of Mental Disorders, Fourth Edition) Autoquestionnaire CHQ (Chinese Health Questionnaire)	High frequency of axis 1 psychiatric diagnoses (36,4%)
Meyer Bahlburg et al. (2008)*	Not precised	N = 142 women Age not precised CAH-SV (n=21), SW (n=39), NC (n=82)	Control group (n = 23)	Semi-structured interviews : DSM-IV GAF (Global Assessment of Function)	CAH-SW women showed significantly increased depression and anxiety in comparison to controls
Mueller et al. (2010), USA	Hospital Multicentric between 2002 and 2009 PR : 100%	N = 72 patients Age 8-18 years CAH (n = 54 ; 33 men and 21 women) FMPP (n = 18)	Healthy data issued from general population Chronic disease population estimates (epilepsy and diabetes) obtained from another study	Semi-structured interviews : K-SADS P-L (Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version)	24 patients with CAH (44%) met the criteria for at least one psychiatric diagnosis lifetime CAH females showed significantly increased rate of anxiety relative to healthy adolescent females (p=0;02) Trend for lifetime mood disorders for CAH-SW versus CAH-SV (p=0,06)

<p>Engberg et al. (2015), Sweden</p>	<p>Swedish nationwide registers linked with the national CAH register (girls and women with CAH due to 21-hydroxylase deficiency born between 1915 and 2010)</p>	<p>N = 335 women Median age 25,3 years</p> <p>CAH</p> <p>Stratified by phenotypes (SW ; SV and NC or Non-Classical type)</p> <p>Stratified by CYP1A2 genotype (null, 12splice, I172N and P30L)</p>	<p>Matched control group of women</p> <p>Matched control group of men</p>	<p>Use of nationwide registers data (containing discharge diagnoses for all psychiatric inpatient episodes since 1973 and from psychiatric out-patient care since 2001)</p> <p>Evaluation of suicidality : Diagnosis of suicidal attempt</p> <p>Complete suicide frequency (data extracted from the Cause of Death Register)</p>	<p>Girls and women with CAH have significantly twice as likely to have any psychiatric disorder (specifically stress-related and adjustment disorders, psychoactive substance use and alcohol misuse)</p> <p>Higher scores in CAH-SW phenotype</p> <p>When broken down by age, only sub-group of women ≥ 18 years remain significant</p> <p>High risk of psychotic disorder and personality disorder in patients with P30L genotype</p> <p>No increase of suicide attempt or complete suicide frequency</p>
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CAH-SV : Congenital Adrenal Hyperplasia simple-virilizers ; CAH-SW : CAH with salt wasting syndrome ; FMPP : Familial Male Precocious Puberty

**datas from abstract*

Table 3 : Methodologies and principal results from studies evaluating women suffered from malformative etiologies of DSD

Reference	Recruitment and participation rate (PR)	DSD sample	Control group	Main criterion and evaluation	Results
Morgan et al. (2006), USA	Hospital Electronic records at the University of Michigan Health Systems (UMHS) gynecologic clinic between 1998 and 2003 PR : 100%	N = 7 women Age : 18 à 35 years Vaginal agenesis	No control group	Self-reports : BSI (Brief Symptom Inventory) Measure on self-esteem : RSES (Rosenberg Self-Esteem Scale) Emotional response to diagnosis evaluated by specific questions	5 have never had any counseling or been on psychiatric medication For 3 patients GSI (Global Severity index) indicate the presence of current symptoms of poor psychological functioning Average levels of self-esteem Emotional response to diagnosis : confusion, depression, shame, shock
Laggari et al. (2008), Greece	Hospital PR : 100%	N = 5 women with MRKHS Mean age : 18 years Total sample = 27 (associated sample study including patients with PCOS because the aim is to assess consequences of Primary Amenorrhea)	Matched control group (n = 27)	Self-reports : BDI (Beck Depression Inventory) STAI-Gr (State-Trait Anxiety Inventory) SLEC (Stressful Life Events Chedule)	Significantly higher scores than control group on the STAI-Gr ($p \leq 0,05$) Significantly higher scores on BDI after adjustment on stressful life events (OR =1,19) and socio-economic status (OR = 1,19, $p \leq 0,05$) (significance disappear after adjustment for chronological age)

<p>Heller-Boersma et al. (2009), England</p>	<p>Hospital PR : 20%</p>	<p>N = 66 women Mean age : 27,9 years MRKHS (mean time since diagnosis : 10 years)</p>	<p>Control group (n = 31)</p>	<p>Self-reports : SCL-90 R RSES IIP-32 (Inventory of Interpersonal Problems) EDI (Eating Disorder Inventory)</p>	<p>On the SCL-90-R : significantly higher scores on the subscales Phobic Anxiety and Psychoticism (interpersonal alienation) (respectively, $p=0,020$ and $0,007$) and trend for the subscale Depression ($p=0,089$) and Anxiety ($p=0,087$) Significantly decreased self-esteem ($p=0,007$) Significantly higher scores on total EDI ($p=0,018$), precisely on sub-scales "interoceptive awareness", "ineffectiveness", interpersonal distrust", and "bulimia" (all $p \leq 0,05$)</p>
<p>Lih-Mei Liao et al. (2011), England</p>	<p>Hospital (multidisciplinary clinic in a tertiary referral service for adults with DSD over a 2 years period) PR : 64%</p>	<p>N = 56 women Median age : 21,7 years (18-52 years) MRKHS</p>	<p>Normative data from general population</p>	<p>Self-reports : HADS (Hospital Anxiety and Depression Scale)</p>	<p>Higher mean scores for anxiety than the standardization sample ($p=0,02$) No significant difference for depression ($p=0,64$)</p>

MRKHS : Meyer-Rokitansky-Kuster-Hauser Syndrome