RESEARCH

Health status in 1040 adults with disorders of sex development (DSD): a European multicenter study

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Abstract

Objective: The knowledge about health status in adults with disorder of sex development (DSD) is scarce.
Design and methods: A cross-sectional observational study in 14 European tertiary centers recruited 1040 participants (717 females, 311 males, 12 others) with DSD. Mean age was 32.4 ± 13.6 year (range 16–75). The cohort was divided into: Turner ($n = 301$), Klinefelter ($n = 224$), XY-DSD ($n = 222$), XX-DSD (excluding congenital adrenal hyperplasia (CAH) and 46,XX males) ($n = 21$), 46,XX-CAH ($n = 226$) and 45,X/46,XY ($n = 45$). Perceived and objective health statuses were measured and compared to European control data.
Results: In DSD, fair to very good general health was reported by 91.4% and only 8.6% reported (very) bad general health (controls 94.0% and 6.0%, $P < 0.0001$). Longstanding health issues other than DSD and feeling limited in daily life were reported in 51.0% and 38.6%, respectively (controls 24.5% and 13.8%, $P < 0.0001$ both). Any disorder except DSD was present in 84.3% (controls 24.6%, $P < 0.0001$). Males reported worse health than females. In the subgroup analysis, Klinefelter and 46,XX-DSD patients reported bad general health in 15.7% and 16.7%, respectively (Turner 3.2% and CAH 7.4%). Comorbidities were prevalent in all DSD subgroups but Klinefelter and Turner were most affected. Early diagnosis of DSD and a healthy lifestyle were associated with less comorbidities.
Conclusions: Overall, general health appeared to be good but a number of medical problems were reported, especially in Klinefelter and Turner. Early diagnosis of DSD and a healthy lifestyle seemed to be important. Lifelong follow-up at specialized centers is necessary.

Key Words

- congenital adrenal hyperplasia
- Klinefelter syndrome
- Turner syndrome
- age at diagnosis
- healthy lifestyle
- psychiatric
- suicide
- cardiovascular
- metabolic
- comorbidities

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Introduction

Disorders of sex development (DSD) are characterized by incongruence of chromosomal, gonadal and genital sex development, and in some conditions, impaired adrenal function. DSD can be divided into three major groups: DSD with atypical sex chromosome configurations such as Turner syndrome (TS), Klinefelter syndrome (KS), 45,X/46,XY and 46,XX/46,XY; XY-DSD characterized by impairment of testicular development, androgen biosynthesis or action or severe hypospadias of unknown origin; and XX-DSD characterized by androgen excess such as congenital adrenal hyperplasia (CAH) (1). Due to the wide range of pathophysiology and presentation, patients with DSD may need a large variety of treatments such as genital surgery, sex hormone replacement, glucocorticoid supplementation and other treatments, which beside the underlying cause also may affect the health status, both somatically and mentally. However, knowledge about the health status in individuals with DSD, especially adults, is scarce. For example, for the rare XY-DSD conditions, almost no data on health status are available except that there is a high prevalence of decreased bone mineral density in CAIS women (2, 3). The vast majority of reports have been published on the three larger groups of DSD, namely TS, KS and CAH. These reports have indicated increased risks of congenital abnormalities in TS, cardiometabolic risk factors and diseases mostly related to treatment, autoimmune disorders, tumors and psychiatric disorders in addition to decreased bone health with increased fracture incidence for all groups (4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21). A healthy lifestyle can modify and prevent many of these comorbidities but how the persons with DSD perceive their general health may differ from the perception of their treating physicians. Moreover, it could be speculated that a late diagnosis of DSD may result in a more compromised health status. Undiagnosed low sex hormone levels during adolescence may affect peak bone mass (3), while high androgen levels may affect voice and insulin sensitivity in females (22). Thus, more data on the health status in individuals with a DSD are needed, including modifying factors, to be able to predict, prevent and manage different health outcomes, in addition to plan specialized services for this group of patients.

The aim of this study was to describe the health status of the whole dsd-LIFE cohort by evaluating comorbidities, cardiovascular and metabolic risk factors, healthy lifestyle and age at diagnosis.

Subjects and methods

This study is part of the dsd-LIFE study (23). Patients, aged 16 years and older with a medically confirmed clinical and/or genetic diagnosis of DSD, were recruited from 14 sites, including Berlin, Munich, Lubeck and Munster (Germany); Paris, Lyon, Montpellier and Toulouse (France); Amsterdam and Nijmegen (The Netherlands); Lodz and Warsaw (Poland); Stockholm (Sweden) and Birmingham (UK). Control data were obtained from Eurostat (total $n>200{,}000$; females $n>100{,}000$; males $n>100{,}000$, year 2014) (http://ec.europa.eu/eurostat/web/health/overview), except in five conditions where no data were available, i.e., psychiatric disorders, suicide attempts, hypertension, dyslipidaemia and autoimmune disorders (only thyroid disorders) where controls were obtained from Swedish CAH studies with similar age and gender distribution as the dsd-LIFE study (total $n=58{,}800$; females $n=33{,}500$; males $n=25{,}300$) (16, 18, 24).

Study protocol

The complete study protocol has been published in detail previously by Röhle *et al.* (23). In summary, subjects underwent a medical examination, including questions about the medical history and answered a patient reported outcome questionnaire. The participation rate was 36.1% of those contacted, the genetic diagnosis rate was 78.6% of the total and 55.6% of those with non-sex chromosome DSD, the patient reported outcome questionnaire response rate was 95.5%, medical history was supplied by 99.5% and examination was done in 89.2%. Data were entered anonymously into a database. Healthy lifestyle, age at diagnosis, cardiovascular and metabolic risk factors and comorbidity were evaluated. A healthy lifestyle was defined as never smoked in combination with sport activities ≥2 h/week. Participants were asked to rate their general health as good/very good, fair or bad/very bad. For cardiovascular and metabolic risk factors, the following variables were evaluated: body mass index (BMI) (overweight 25–29.9 and obesity ≥30 kg/m^2); waist/hip ratio (central obesity ≥0.8 in females and ≥0.9 in males, respectively); hypertension (blood pressure >140/90 mmHg); type 2 diabetes; dyslipidaemia and cardiovascular disease (history of heart attack, stroke, venous thromboembolism, arrhythmias, coarctation of the aorta, bicuspid aortic valve or aortic stenosis). For the description of comorbidities, the following

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variables were used: psychiatric disorders (eating disorder, chronic anxiety, chronic depression, attention problems, hyperactivity, eruptive/aggressive behaviour, burn-out-syndrome, schizophrenia, autism, Asperger or pervasive developmental disorder, other mental health problems and/or suicide attempt); gastrointestinal disorders (fatty liver disease, hepatitis, elevated liver enzymes, Crohn's disease/colitis and/or celiac disease); autoimmune disorders (Hashimoto's thyroiditis, type 1 diabetes, rheumatology disease, Crohn's disease/colitis, celiac disease, allergies and/or asthma); joint problems (rheumatic disease and/or other joint problems); renal disorders (horseshoe kidney and/or renal insufficiency); malignancy; visual and hearing issues; neurological disorders (seizures and/or migraine); urinary issues (urinary tract infections and/or incontinence) and any disorder except DSD was defined as any of the disorders or problems above (except overweight and obesity), calculated with both visual issues included and excluded.

The study was approved by the Local Ethical Review Board at each participating center, and informed consent was obtained (23).

Statistical analysis

Mean ± S.D. or median (range) is reported for continuous variables, and absolute and relative frequencies for categorical outcomes. All proportions were calculated discounting missing values. Continuous variables were compared using *t*-tests, and categorical parameters were compared using chi-squared tests or Fisher exact tests, whichever most appropriate. Logistic regression models were used to explore the associations between different outcomes and age at diagnosis and healthy lifestyle. When odds ratios (ORs) were calculated, 95% confidence intervals (CIs) were reported. Due to the exploratory nature of dsd-LIFE, no adjustments for multiple comparisons were done. R (version 3.2.2) and SAS (version 9.4) were used for all statistical analyses.

Results

The results are shown in detail for the total cohort and for phenotypic females and males in Tables 1 and 2, broken down by subgroup in Tables 3 and 4 and logistic regression models in Table 5. In Supplementary Table 1 (see section on supplementary data given at the end of this article), the number of individuals for each variable is shown.

Basic characteristics of the patients

In total, 1161 patients were evaluated in dsd-LIFE cohort, but males with CAH ($n=121$) were excluded in the present analyses since they did not fulfill the complete criteria for a DSD diagnosis (23). Thus, 1040 patients were included with a mean age range of 32.4 ± 13.6 years. The different DSD diagnoses and the six major subgroups of the cohort are described in Table 1. One 47,XYY male was not included in any of the subgroups. The number of females was more than twice the number of males and the mean age about 4 years younger in females. Moreover, the mean age at diagnosis of the DSD condition was 8 years earlier in females (Table 2).

Lifestyle and general health

Around 15% in the whole DSD cohort was currently smoking, which was less than controls (Table 2). None of the XX-DSD individuals and only around 7% of individuals with TS or 45,X/46,XY smoked (Table 3). Sport activities per week, varied in the different groups and differed from controls. Especially the XY-DSD males seemed to be very active (Table 4). Of the entire cohort 91.4% reported a fair to good/very good general health and only 8.6% reported bad or very bad general health, which was worse compared to controls. Males with DSD reported worse health compared to females with DSD (15.2% vs 5.6%). General health was worse compared to controls in all subgroups except in XY-DSD females, XX-DSD and 45,X/46XY. Longstanding health issues other than the DSD diagnosis were reported in about half the cohort with physical issues being most common. This was more than that in controls in all groups except XY-DSD males and XX-DSD. In general, males had more physical and psychiatric problems than females. Individuals with KS reported most longstanding health problems (62.4%). Almost half of all males felt limited in their daily life by health issues and the KS group was the subgroup that experienced the most limitations while only around 14% of controls reported limitations. The composite endpoint 'Any disorder except DSD' was present in 84.3% of all cases, and in 94.5% of individuals with TS. Similar percentages were found when visual issues were excluded. This was 2–3 times more than those in controls.

Cardiovascular and metabolic disorders

Mean BMI was 25.5 kg/m^2 in the entire cohort and 17.2% were obese (controls 14.8%). Males were more often

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Table 1 The specific diagnoses of the 1040 patients with DSD, their subgroup classification and sex.

	Females	Males	Other	Total
Turner syndrome				**301**
Monosomy: 45,X	150			
Mosaics: 45,X/46,XX	31			
Isochromosomes: 45,X/46,X,i(Xq)|46X,i(Xq)|45,X/46,X,i(Xq)/47,X,i(Xq)	59			
Deletions: 45,X/46,X,del(X)|46,X,del(X)	19			
Polyploidy: 45,X/46,XX/47,XXX|45,X/47,XXX|45,X/46,XX/47,XXX/48,XXXX	16			
Ring material: 45,X/46,X,r(X)	12			
Others and unknown	14			
Klinefelter syndrome				**224**
47,XXY	1*	199	4	
47,XXY/46,XY		5	1	
47,XXY/46,XX		3		
Others and unknown		5		
46,XX testicular males		6		
XY-DSD				**222**
Complete gonadal dysgenesis	20		1	
Partial gonadal dysgenesis	12	25		
XY ovotesticular DSD	3	2		
CAIS	69		2	
PAIS	17	18		
3β-HSD deficiency	1	1		
17β-HSD deficiency	9		2	
5α-reductase deficiency	2	1	1	
17α-hydroxylase/17,20 lyase deficiency	1			
Unknown steroid synthesis defect with adrenal insufficiency	1			
Unknown androgen synthesis defect		1		
Hypospadias		24	1	
Others and unknown	7	1		
XX-DSD				**21**
XX gonadal dysgenesis	20			
XX ovotesticular DSD	1			
CAH				**226**
Salt-wasting 21OHD***	109	2**		
Simple virilising 21OHD***	65	1**		
Non-classical 21OHD***	33	1**		
Unknown phenotype 21OHD	3			
STAR	1			
3β-HSD deficiency	2			
11β-hydroxylase deficiency	5	1**		
POR deficiency	2			
Unknown	1			
45,X/46,XY	31	14		**45**
47,XYY with gonadal dysgenesis		1		**1**
Total	**717**	**311**	**12**	**1040**

Males with 46,XY-CAH were excluded ($n=121$) since they did not fulfil all criteria of DSD. STAR, CAH caused by mutations in the steroidogenic acute regulatory protein gene, i.e., congenital lipoid adrenal hyperplasia.
*Had sex reassignment in adulthood; **46,XX; ***Mainly based on the predicted phenotype from genotype data.
21OHD, 21-hydroxylase deficiency; CAH, congenital adrenal hyperplasia; CAIS, complete androgen insensitivity syndrome; HSD, hydroxysteroid dehydrogenase; PAIS, partial androgen insensitivity syndrome; POR, cytochrome P450 oxidoreductase.

overweight and almost 60% of KS patients were either overweight or obese (male controls 54.8%) (Tables 2 and 3). More than 50% of the CAH patients were overweight or obese (38.8% female controls). However, the proportion of individuals with underweight (BMI <20 kg/m^2) was also higher in the DSD groups compared to controls. Using the different waist/hip ratio cut-off levels for females and males indicated that the health risk in females with DSD was higher, especially in the XX-DSD subgroup. Type 2 diabetes was present in 4.1% of all patients and was more prevalent in the male group (6.9%), which was higher than that in controls (1.7%). There were large differences

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in the prevalence of type 2 diabetes between the subgroups with 9.1% affected in the KS and only 1.5% in the XY-DSD subgroup. Hypertension was more prevalent compared to controls except in the XY-DSD female and XX-DSD groups. Dyslipidemia was more common compared to controls in all groups except in the XX-DSD. Dyslipidemia was especially prevalent in individuals with KS (19.9%). Around 15% of DSD had at least one cardiovascular disease (controls 5%), 3.1% two and 0.8% had three or more diagnoses with no differences between females and males. In the subgroups, cardiovascular disease was especially prevalent in the TS group, 45,X/46,XY and KS groups; however, the only subgroup with no increase compared to controls were phenotypically females with XY-DSD or XX-DSD.

Other comorbidity

Psychiatric disorders were reported in 45.2% and suicide attempt in 6.8% of all individuals with DSD and more males than females were affected (Table 2). Especially individuals with KS were affected, but all groups were more affected compared to controls (Tables 3 and 4). The prevalence of osteoporosis and fractures were similar between females and males, however, also here, individuals with KS were most affected. Gastrointestinal disorders were more prevalent in females with DSD overall and in TS (more compared to controls in most groups). Autoimmune disorders were present in a third of the entire DSD cohort (TS 45.2% and KS 43.3%) and equally common in both females and males, which was more than those in controls. Joint problems were more common in males with DSD overall and in KS. Renal disorders were most prevalent in females with DSD overall and in TS, mainly due to congenital horseshoe kidney in the latter. Malignancy had occurred in 4.1% and was more common than in controls in all groups except XY-DSD males, XX-DSD and 45,X/46,XY. Visual and hearing issues were prevalent, and most affected were patients with TS. Neurological disorders, i.e., seizures and/or migraine were most frequent in KS. Urinary issues were not different between the sexes, but XY-DSD and CAH were the most affected subgroups (no control data).

Logistic regression models

Using logistic regression models, there were significant associations between any long-standing health problem, health issues that limited daily life, any disorder except DSD and age at diagnosis of the DSD (Table 5). Similar relationships were also found with healthy lifestyle. There was only a tendency for obesity and age at diagnosis but an association was found with healthy lifestyle (OR 0.32). However, there was a positive correlation with age at diagnosis and BMI (R=0.03 per year, P<0.0001). Type 2 diabetes, hypertension and dyslipidemia were associated with the age at diagnosis (OR 1.05, 1.03 and 1.04, respectively). Thus, a diagnosis of DSD at 10 years or 40 years compared to at birth increased the odds for type 2 diabetes with 63% (OR 1.63) and 604% (OR 7.04), respectively. Type 2 diabetes and dyslipidemia were less common with a healthy lifestyle (OR 0.20 and 0.62, respectively). Cardiovascular disease was associated with the age at diagnosis (OR 1.03) but not healthy lifestyle. Psychiatric, autoimmune and neurological disorders (OR 1.02, 1.02 and 1.03, respectively), joint and urinary issues (OR 1.03 and 0.96, respectively) were all associated with age at diagnosis. Among these disorders, healthy lifestyle was only associated with psychiatric disorders (OR 0.29). Similar results were found for the different subgroups and age at diagnosis and healthy lifestyle, respectively, but mostly not significant (data not shown). However, there was a relationship between age at diagnosis and age at inclusion in dsd-LIFE (Fig. 1) explaining some (28.8%) but not all outcomes related to age at diagnosis (R=0.537, P<0.0001).

Discussion

This is by far the largest study examining the health status in individuals diagnosed with DSD but also the first to include the majority of conditions encompassed by the DSD classification. The patients reported a good or fair general health in more than 91% of the cases and less than 9% reported bad or very bad general health. In general, males reported worse health than females but both males and females reported poorer health compared to European control data. Longstanding health issues other than DSD were reported by half of the individuals with men more often reporting both physical and psychiatric comorbidities compared to women. However, if all the different disorders, other than DSD, reported by the individuals themselves or the examining physicians were assessed together more than 80% had at least one additional comorbidity, which was 2–3 times more common than for controls. Thus, individuals with DSD

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Table 2 Characteristics and health status in the 1040 patients with DSD compared to controls.

	All DSD ($n=1040$)$^{\alpha}$	Controls$^{€}$ ($n>200000$)	*P* value	Female DSD ($n=717$)$^{\alpha}$	Female controls$^{€}$ ($n>100000$)	*P* value	Male DSD ($n=311$)$^{\alpha}$	Male controls$^{€}$ ($n>100000$)	*P* value	*P* value F vs M DSD
Age (years)	32.4 ± 13.6	16–64		30.9 ± 12.3	16–64		35.0 ± 15.4	16–64		**<0.0001**
Age at diagnosis (years)	10 (0–68)			7.5 (0–61)			16 (0–68)			**<0.0001**
Smoking	14.5%	22.3%	**<0.0001**	13.3%	18.5%	**0.0005**	16.2%	26.2%	**0.0001**	0.2905
Sports activities (cycling, swimming etc.)			**<0.0001**			**<0.0001**			0.1501	**0.0456**
<2 h/week	50.6%	44.7%		53.3%	47.7%		44.9%	41.6%		
2 h/week	15.4%	22.0%		15.7%	23.5%		15.5%	20.5%		
>2 h/week	34.0%	33.2%		31.1%	28.7%		39.6%	37.9%		
How is your health in general?			**<0.0001**			**<0.0001**			**<0.0001**	**<0.0001**
Very good/Good	62.7%	76.5%		66.7%	74.9%		54.1%	78.1%		
Fair	28.7%	17.5%		27.7%	18.9%		30.7%	16.1%		
Bad/Very bad	8.6%	6.0%		5.6%	6.2%		15.2%	5.8%		
Longstanding health problem?*	51.0%	24.5%	**<0.0001**	49.4%	26.0%	**<0.0001**	53.7%	23.0%	**<0.0001**	0.2623
Physical?	91.5%			91.0%			92.9%			**0.0063**
Psychiatric?	27.5%			23.4%			34.3%			
Both?	19.0%			14.4%			27.3%			
Health issues limited daily life, past 6 m	38.6%	13.8%	**<0.0001**	33.3%	15.0%	**<0.0001**	48.5%	12.5%	**<0.0001**	**<0.0001**
BMI (kg/m^2)	25.5 ± 5.7			25.4 ± 5.9			25.8 ± 5.3			0.3694
<20 kg/m^2	14.1%	3.2%	**<0.0001**	14.9%	4.6%	**<0.0001**	12.8%	1.7%	**<0.0001**	**0.0279**
20–24.9 kg/m^2	40.5%	50.1%		42.5%	56.5%		35.2%	43.5%		
25–29.9 kg/m^2	28.2%	32.5%		25.4%	25.2%		34.5%	40.0%		
≥30 kg/m^2	17.2%	14.5%		17.2%	13.6%		17.4%	14.8%		
W/H ratio	0.78 ± 0.13			0.78 ± 0.14			0.79 ± 0.11			0.2136
W/H ratio >0.8 (F) >0.9 (M)	23.2%			27.8%			14.9%			**0.0008**
Type 2 diabetes	4.1%	1.7%	**<0.0001**	3.1%	1.5%	**0.0023**	6.9%	1.9%	**<0.0001**	**0.0135**
Hypertension	11.0%	1.8%	**<0.0001**	9.7%	1.7%	**<0.0001**	13.7%	1.9%	**<0.0001**	0.0926
Dyslipidaemia	8.3%	0.4%	**<0.0001**	5.5%	0.3%	**<0.0001**	15.0%	0.5%	**<0.0001**	**<0.0001**
CV disease	15.3%	5.0%	**<0.0001**	14.9%	4.8%	**<0.0001**	16.3%	5.2%	**<0.0001**	0.3242
CV diseases ≥2	3.1%			3.6%			1.6%			
CV diseases ≥3	0.8%			0.6%			1.2%			
Psychiatric dis	45.2%	10.6%	**<0.0001**	41.3%	11.2%	**<0.0001**	52.9%	9.8%	**<0.0001**	**0.0011**
Suicide attempt	6.8%	1.8%	**<0.0001**	5.0%	2.0%	**<0.0001**	10.7%	1.1%	**<0.0001**	**0.0050**
Prefer not to answer	3.9%			4.0%			3.8%			
Osteoporosis	10.7%			9.7%			11.5%			0.4854
Fractures	12.1%			10.8%			13.8%			0.2298
GI disorders	11.0%	2.0%**	**<0.0001**	12.6%	2.0%**	**<0.0001**	7.7%	2.0%**	**<0.0001**	**0.0445**
Autoimmune dis	33.9%	1.1%	**<0.0001**	33.5%	1.7%	**<0.0001**	34.8%	0.3%	**<0.0001**	0.7661
Joint problems	10.6%	7.5%	**0.0006**	8.7%	8.4%	0.781	13.9%	6.7%	**<0.0001**	**0.0234**
Renal dis	4.5%	2.0%**	**<0.0001**	5.6%	2.0%**	**<0.0001**	1.9%	2.0%**	1	**0.0209**
Malignancy	4.1%	0.7%	**<0.0001**	4.5%	0.8%	**<0.0001**	2.9%	0.5%	**<0.0001**	0.3675

Visual issues	26.2%	1.9%	**<0.0001**	27.3%	2.1%	**<0.0001**	23.4%	1.8%	**<0.0001**	**<0.0001**	0.2468
Hearing issues	18.2%	1.2%	**<0.0001**	22.8%	1.0%	**<0.0001**	7.2%	1.3%	**<0.0001**	**<0.0001**	**<0.0001**
Neuro dis***	11.9%	2.1%	**<0.0001**	10.3%	2.8%	**<0.0001**	14.9%	1.3%	**<0.0001**		0.0559
Urinary issues	13.2%			13.6%			13.0%				0.8741
Any disorder*	84.3%	24.6%	**<0.0001**	85.5%	26.0%	**<0.0001**	80.9%	23.1%		**<0.0001**	0.0905

Mean ± S.D. is given. Bold indicates $P<0.05$.

[α]Of all individuals 68.9% defined themselves as females, 29.9% as males and 1.2% ($n=12$) did not want to define themselves as either female or male. *Except the DSD. **In controls, this is the percentage of combined gastrointestinal and renal disorders. ***Neurological disorders in this case seizures and/or migraine. [€]Control data were from Eurostat (total $n>200,000$; females $n>100,000$; males $n>100,000$) (http://ec.europa.eu/eurostat/web/health/overview), except in five conditions where no data were available, i.e., Psychiatric disorders, Suicide attempts, Hypertension, Dyslipidaemia and Autoimmune disorders (only thyroid disorders) where controls were from Swedish CAH studies with similar age and gender distribution as the dsd-Life study (total $n=58,800$; females $n=33,500$; males $n=25,300$) (18, 20, 26).

CV, cardiovascular; dis, disorders; F, phenotypically females; GI, gastrointestinal; M, phenotypically males; W/H, waist/hip.

did not consider many of their comorbidities as major concerns. The finding that less than 40% responded that health issues had limited their daily life also supports this conclusion.

Cardiovascular and metabolic disorders were common in our cohort, which have previously been shown separately in TS, KS and CAH (5, 7, 16). It has been suggested that TS is an independent risk factor for cardiovascular disease leading to congenital heart disease, aortic dilation and dissection, valvular heart disease, hypertension, thromboembolism, myocardial infarction and stroke (5). Even though TS had the highest frequency of cardiovascular disease in our study, the frequency was almost as high in the group of 45,X/46,XY followed by the KS group. However, women with TS are often affected by congenital heart disease not seen in, e.g., KS and CAH (7, 16). A study of 16 children with 45,X/46,XY found increased risk of cardiac anomalies and other features of TS, and thus, recommended that 45,X/46,XY patients should have similar follow-up (25). However, our study suggests that all different DSD variants (except XY-DSD females and XX-DSD) may have increased cardiometabolic issues to some degree and should be monitored and treated accordingly.

Psychiatric disorders were prevalent, especially in KS. Similar rates have previously been reported in KS (7) and increased rates, however, not as high as in this study have also been reported in CAH (18, 24). The high rate of suicide attempts is of great concern. Moreover, some individuals (3.9%) preferred not to answer this question, which may for some, reflect that they had made a suicide attempt previously but did not want to disclose this or that they had had suicidal thoughts. Suicide and attempts have hardly been studied previously in DSD. In a Swedish registry study, females with CAH had a lower suicidal rate than the controls (0.9% vs 2%) (18), while in males with CAH, the rate was higher than in controls (2.8% vs 1.2%) (24), thus, much lower than the 6% found among the individuals with CAH in the present study. Probably this reflects that the current study reports on self-reported suicidality while the previous registry studies gave diagnosis rates.

Reported osteoporosis and fractures were rather common despite the young age of the cohort. Especially individuals with TS and KS were affected, which has previously been attributed mainly to hypogonadism and also to X-chromosome abnormalities (4, 7). This needs to be investigated in more detail in future studies. In CAH, the use of glucocorticoids may further increase the risk (22), but in the present study, individuals with

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Table 3 Characteristics and health status of the patients in the six major subgroups of DSD compared to controls.

	Turner (*n* = 301)	*P* value vs F controls	Klinefelter (*n* = 224)	*P* value vs M controls	XY DSD (*n* = 222)	*P* value vs all controls	XX DSD (*n* = 21)	*P* value vs F controls	CAH (*n* = 226)	*P* value vs F controls	45,X/46,XY (*n* = 45)	*P* value vs all controls	*P* value different DSDs
Age (years)	32.2 ± 13.3		39.6 ± 15.1		28.8 ± 12.2		22.9 ± 5.2		30.4 ± 11.4		28.8 ± 12.3		**<0.0001**
Age at diagnosis (years)	10 (0–56)		22 (0–68)		4 (0–61)		15 (0–19)		0 (0–56)		7 (0–51)		**<0.0001**
Females	100%		0.4%		64.0%		100%		97.8%		68.9%		**<0.0001**
Males	0%		97.3%		32.9%		0%		2.2%		31.1%		
Other sex	0%		2.2%		3.2%		0%		0%		0%		
Smoking	7.3%	**<0.0001**	19.5%	**0.0437**	17.7%	0.1402	0%	0.088	18.6%	1	7.5%	**0.0218**	**0.0004**
Sports activities (cycling, swimming etc)		**0.0018**		**0.0433**		**<0.0001**		0.4614		**0.0463**		0.1472	**0.0009**
<2 h/week	58.6%		50.0%		37.2%		58.3%		52.0%		60.0%		
2 h/week	16.5%		15.1%		14.7%		8.3%		16.3%		11.4%		
>2 h/week	24.9%		34.9%		48.2%		33.3%		31.6%		28.6%		
How is your health in general?		**<0.0001**		**<0.0001**		**<0.0001**		0.1541		**0.0003**		0.5906	**0.0004**
Very good/good	68.1%		52.9%		63.3%		61.1%		63.4%		72.1%		
Fair	28.7%		31.4%		26.5%		22.2%		29.3%		23.3%		
Bad/very bad	3.2%		15.7%		10.2%		16.7%		7.4%		4.7%		
Longstanding health problem?*	50.2%	**<0.0001**	62.4%	**<0.0001**	35.3%	**0.0006**	43.8%	0.1487	56.2%	**<0.0001**	56.1%	**<0.0001**	**<0.0001**
Physical?	89.3%		93.1%		88.7%		100%		91.7%		100%		**0.0349**
Psychiatric?	27.0%		44.9%		35.5%		33.3%		8.3%		9.5%		
Both?	16.2%		28.3%		24.2%		33.3%		10.0%		9.5%		
Health issues limited daily life, past 6 m	31.5%	**<0.0001**	55.2%	**<0.0001**	35.1%	**<0.0001**	21.4%	0.4549	38.4%	**<0.0001**	32.5%	**0.002**	**<0.0001**
BMI (kg/m^2)	25.4 ± 5.3		26.1 ± 5.3		24.1 ± 6.0		21.8 ± 4.2		26.4 ± 6.2		26.7 ± 5.5		**<0.0001**
<20 kg/m^2	10.1%	**<0.0001**	10.4%	**<0.0001**	24.9%	**<0.0001**	40.0%	**<0.0001**	10.9%	**<0.0001**	11.4%	**0.0017**	**<0.0001**
20–24.9 kg/m^2	47.2%		31.3%		42.9%		50.0%		38.0%		34.1%		
25–29.9 kg/m^2	26.2%		40.8%		20.5%		5.0%		28.5%		29.5%		
≥30 kg/m^2	16.4%		17.4%		11.7%		5.0%		22.6%		25.0%		
W/H ratio	0.74 ± 0.13		0.80 ± 0.11		0.80 ± 0.12		0.85 ± 0.20		0.79 ± 0.13		0.77 ± 0.14		**0.0002**
W/H ratio >0.8 (F) >0.9 (M)	16.4%		16.6%		26.9%		50.0%		33.6%		18.2%		**0.0008**
Type 2 diabetes	4.3%	**0.0013**	9.1%	**<0.0001**	1.5%	1	5.0%	0.2610	2.3%	0.2661	2.3%	0.5298	**0.0026**
Hypertension	13.5%	**<0.0001**	15.7%	**<0.0001**	4.9%	**0.0043**	0%	1	7.7%	**<0.0001**	22.7%	**<0.0001**	**0.0001**
Dyslipidaemia	7.5%	**<0.0001**	19.9%	**<0.0001**	5.0%	**<0.0001**	0%	1	3.7%	**<0.0001**	4.7%	**0.0131**	**<0.0001**
CV disease	23.0%	**<0.0001**	17.9%	**<0.0001**	8.5%	**0.008**	0%	0.6229	10.0%	**0.0002**	22.0%	**<0.0001**	**<0.0001**
CV diseases ≥2	6.5%		1.7%		1.0%		0%		0.9%		9.8%		
CV diseases ≥3	1.4%		1.7%		0%		0%		0%		0%		
Psychiatric dis	39.7%	**<0.0001**	59.0%	**<0.0001**	43.1%	**<0.0001**	50.0%	**<0.0001**	42.3%	**<0.0001**	37.2%	**<0.0001**	**0.0005**
Suicide attempt	2.8%	0.2673	12.9%	**<0.0001**	7.4%	**<0.0001**	5.6%	0.2765	6.0%	**0.0003**	4.7%	0.1749	**0.0076**
Prefer not to answer	4.6%		4.3%		2.8%		11.1%		3.3%		2.3%		
Osteoporosis	15.8%		16.6%		8.3%		5.0%		2.7%		4.8%		**<0.0001**
Fractures	12.7%		18.4%		12.3%		5.6%		8.6%		2.5%		**0.0182**
GI disorders	24.2%	**<0.0001**	9.8%	**<0.0001**	2.5%	0.6062	0%	**<0.0001**	4.1%	**0.0433**	13.2%	**0.0009**	**<0.0001**
Autoimmune dis	45.2%	**<0.0001**	43.3%	**<0.0001**	25.5%	**<0.0001**	30.0%	**<0.0001**	22.2%	**<0.0001**	20.5%	**<0.0001**	**<0.0001**
Joint problems	7.9%	0.8294	21.0%	**<0.0001**	5.4%	0.2887	0%	0.4064	12.6%	**0.0491**	0%	0.0745	**<0.0001**
Renal dis	12.2%	**<0.0001**	2.6%	0.4259	0.5%	0.1997	0%	1	0.5%	0.1395	2.3%	0.5806	**<0.0001**
Malignancy	5.8%	**<0.0001**	4.2%	**<0.0001**	2.5%	**0.0148**	0%	1	4.5%	**<0.0001**	0%	1	0.2880

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Visual issues	37.1%	**<0.0001**	28.2%	**<0.0001**	20.5%	**<0.0001**	5.3%	0.332	18.4%	**<0.0001**	20.9%	**<0.0001**	**<0.0001**
Hearing issues	47.4%	**<0.0001**	8.1%	**<0.0001**	3.0%	**0.0356**	10.0%	0.0169	2.7%	0.1765	20.9%	**<0.0001**	**<0.0001**
Neuro dis***	6.5%	**0.0013**	20.4%	**<0.0001**	13.9%	**<0.0001**	5.0%	0.4334	11.3%	**<0.0001**	4.7%	0.2283	**0.0001**
Urinary issues	5.8%		7.8%		22.4%		10.5%		19.9%		10.3%		**<0.0001**
Any disorder*	94.5%	**<0.0001**	87.1%	**<0.0001**	75.0%	**<0.0001**	78.9%	**<0.0001**	77.6%	**<0.0001**	81.8%	**<0.0001**	**<0.0001**

Bold indicates $P<0.05$. Control data were from Eurostat (total $n>200,000$; females $n>100,000$; males $n>100,000$) (http://ec.europa.eu/eurostat/web/health/overview), except in five conditions where no data were available, i.e., Psychiatric disorders, Suicide attempts, Hypertension, Dyslipidaemia and Autoimmune disorders (only thyroid disorders) where controls were from Swedish CAH studies with similar age and gender distribution as the dsd-Life study (total $n=58,800$; females $n=33,500$; males $n=25,300$) (18, 20, 26).
*Except the DSD; **in controls this is the percentage of combined gastrointestinal and renal disorders; ***Neurological disorders in this case seizures and/or migraine.
CV, cardiovascular; dis, disorders; F, females; GI, gastrointestinal; M, males; W/H, waist/hip.

CAH were least affected by osteoporosis. However, the fracture rate in CAH was three times higher than the osteoporosis rate. A similar pattern has been seen before in females with CAH (9) and may be due to their interest in rough sport and outdoor activities (26). Since most studies of bone mineral density and fractures in different variants of DSD have occurred in young individuals, it can be predicted that this will be an increasing issue with age.

There have been concerns about tumor risk in DSD, especially increased risk for germ cell tumors if Y-chromosome material is present (however not in KS) (27); breast and lung cancer in addition to non-Hodgkin lymphoma in KS (7, 27); meningioma and childhood brain tumors and possibly bladder cancer, melanoma and corpus uteri cancer in TS (6). We found an increased risk of malignancies. Since some of the gonads may have been removed during early childhood, the patient and physician may not be aware of the histological report; this may be an underestimation.

Most of the other results concerning comorbidities were as expected, for example, an increased risk of gastrointestinal and autoimmune disorders, horseshoe kidneys, visual and hearing issues in TS (5) and many of the individuals in the XY-DSD and CAH groups had had previous genital surgery and had more urinary issues. Neurological disorders (mainly migraine) and joint problems were especially prevalent in KS but also generally in the whole cohort compared to controls.

In particular, in our cohort, the patients with KS reported the worst outcome. They frequently reported bad general health and longstanding health problems, including most comorbidities. It is not uncommon that KS is undiagnosed, in an epidemiological study, only 25% of the expected number of patients was diagnosed, and few were diagnosed before puberty (28). This could imply that the identified patients may be those that are more affected by their disorder or have contracted other disorders or comorbidities. Hence, there is a risk for a selection bias and overrepresentation of individuals with KS with more somatic and psychiatric difficulties in this study. On the other hand, a late diagnosis of KS could also at least partly explain the impaired health status *vide infra*. Interestingly, women with TS had also many disorders such as cardiovascular disorders, renal disorders, in particular horse kidneys and gastrointestinal disorders, i.e. celiac disease, known features of the syndrome, but they still reported better general health, less general health issues and limitations by the disorder than did individuals with KS.

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Table 4 Characteristics and health status in the individuals diagnosed with XY DSD divided into phenotypical females and males compared to controls.

	Female XY DSD ($n=142$)	Female controls€ ($n>100000$)	*P*-value	Male XY DSD ($n=73$)	Male controls€ ($n>100000$)	*P*-value
Age (years)	30.7 ± 12.5	16–64		23.3 ± 7.7	16–64	
Age at diagnosis (years)	13 (0–61)			0 (0–23)		
Smoking	20.8%	18.5%	0.482	7.7%	26.2%	**0.0003**
Sports activities (cycling, swimming etc)			**0.0021**			**0.0067**
<2 h/week	40.5%	47.7%		30.2%	41.6%	
2 h/week	16.5%	23.5%		12.7%	20.5%	
>2 h/week	43.0%	28.7%		57.1%	37.9%	
How is your health in general?			0.1729			**<0.0001**
Very good/Good	68.6%	74.9%		54.4%	78.1%	
Fair	25.0%	18.9%		27.9%	16.1%	
Bad/Very bad	6.4%	6.2%		17.6%	5.8%	
Longstanding health problem?*	35.3%	26.0%	**0.0173**	29.7%	23.0%	0.2333
Physical?	90.0%			87.4%		
Psychiatric?	27.5%			43.7%		
Both?	17.5%			31.2%		
Health issues limited daily life, past 6 m	32.3%	15.0%	**<0.0001**	33.3%	12.5%	**<0.0001**
BMI (kg/m^2)	24.0 ± 6.5			24.4 ± 5.3		
<20 kg/m^2	28.2%	4.6%	**<0.0001**	20.9%	1.7%	**<0.0001**
20–24.9 kg/m^2	40.5%	56.5%		44.8%	43.5%	
25–29.9 kg/m^2	21.4%	25.2%		19.4%	40.0%	
≥30 kg/m^2	9.9%	13.6%		14.9%	14.8%	
W/H ratio	0.81 ± 0.13			0.79 ± 0.11		
W/H ratio >0.8 (F) >0.9 (M)	36.1%			13.6%		
Type 2 diabetes	1.5%	1.5%	0.7225	1.5%	1.9%	1
Hypertension	3.1%	1.7%	0.2889	9.0%	1.9%	**0.0018**
Dyslipidaemia	5.5%	0.3%	**<0.0001**	3.0%	0.5%	**0.0439**
CV disease	6.3%	4.8%	0.2115	13.6%	5.2%	**0.0021**
CV diseases ≥2	0.8%			1.5%		
CV diseases ≥3	0%			0%		
Psychiatric dis	44.3%	11.2%	**<0.0001**	37.7%	9.8%	**<0.0001**
Suicide attempt	7.9%	2.0%	**0.0001**	5.9%	1.1%	**0.0063**
Prefer not to answer	2.9%			2.9%		
Osteoporosis	9.8%			0%		
Fractures	13.8%			4.5%		
GI disorders	3.1%	2.0%**	0.3269	1.5%	2.0%**	1
Autoimmune dis	28.6%	1.7%	**<0.0001**	20.9%	0.3%	**<0.0001**
Joint problems	7.7%	8.4%	0.8752	0%	6.7%	**0.023**
Renal dis	0.8%	2.0%**	0.5266	0%	2.0%**	0.6466
Malignancy	3.1%	0.8%	**0.0207**	1.5%	0.5%	0.2857
Visual issues	23.6%	2.1%	**<0.0001**	15.2%	1.8%	**<0.0001**
Hearing issues	2.3%	1.0%	0.1379	4.5%	1.3%	0.0551
Neuro dis***	18.8%	2.8%	**<0.0001**	3.0%	1.3%	0.2121
Urinary issues	22.0%			25.4%		
Any disorder*	77.5%	26.0%	**<0.0001**	67.2%	23.1%	**<0.0001**

Mean ± S.D. is given. Bold indicates $P<0.05$.

*Except the DSD; **In controls this is the percentage of combined gastrointestinal and renal disorders; ***Neurological disorders in this case seizures and/or migraine. €Control data were from Eurostat (females $n>100,000$; males $n>100,000$) (http://ec.europa.eu/eurostat/web/health/overview), except in five conditions where no data were available, i.e., psychiatric disorders, suicide attempts, hypertension, dyslipidaemia and autoimmune disorders (only thyroid disorders) where controls were from Swedish CAH studies with similar age and gender distribution as the dsd-Life study (total $n=58,800$; females $n=33,500$; males $n=25,300$) (18, 20, 26).

CV, cardiovascular; dis, disorders; GI, gastrointestinal; W/H, waist/hip.

The individuals that reported a healthy lifestyle had a reduced risk of developing psychiatric disorders and also as expected a reduced risk of obesity, type 2 diabetes and dyslipidemia. However, a diagnosis of DSD at an older age was associated with an increase of most health issues. There was also a relationship between age

Table 5 Logistic regression models exploring associations between different outcomes and age at diagnosis and healthy lifestyle (never smoked and sports activities ≥2 h/week) in patients with DSD.

	Age at diagnosis		Healthy lifestyle	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Longstanding health problem?*	1.04 (1.02–1.05)	**<0.0001**	0.47 (0.20–1.09)	0.0853
Health issues limited daily life, past 6 m	1.04 (1.03–1.06)	**<0.0001**	0.68 (0.29–1.61)	0.3702
Obesity	1.01 (1.00–1.03)	0.06782	0.32 (0.12–0.87)	**0.0199**
Type 2 diabetes	1.05 (1.03–1.08)	**0.0002**	0.20 (0.05–0.81)	**0.0214**
Hypertension	1.03 (1.02–1.04)	**0.0003**	0.71 (0.22–2.81)	0.8245
Dyslipidaemia	1.05 (1.02–1.07)	**<0.0001**	0.62 (0.41–0.92)	**0.0192**
CV disease	1.03 (1.01–1.03)	**<0.0001**	0.87 (0.58–1.27)	0.4728
Psychiatric disorders	1.02 (1.00–1.03)	**0.0119**	0.29 (0.12–0.66)	**0.0033**
Osteoporosis	1.06 (1.04–1.08)	**<0.0001**	1.64 (0.39–11.39)	0.5460
Fractures	1.04 (1.02–1.05)	**<0.0001**	0.80 (0.30–2.40)	0.6710
Autoimmune disorders	1.02 (1.01–1.03)	**0.0064**	1.08 (0.47–2.64)	0.9763
Joint problems	1.03 (1.01–1.05)	**0.0046**	0.85 (0.23–4.20)	0.7008
Visual issues	1.01 (1.00–1.03)	0.0565	5.69 (1.62–36.11)	**0.0207**
Hearing issues	1.01 (0.99–1.02)	0.2777	0.39 (0.16–1.00)	**0.0469**
Neurological disorders	1.02 (1.00–1.04)	**0.0287**	0.51 (0.16–2.00)	0.1153
Urinary issues	0.96 (0.94–0.98)	**0.0006**	0.55 (0.18–2.08)	0.3289
Any disorder*	1.04 (1.02–1.06)	**0.0002**	0.31 (0.07–0.93)	**0.0003**

The higher OR the higher risk per each year later the DSD diagnosis was made. Healthy lifestyle was compared to those with not having a healthy lifestyle. Bold indicates $P<0.05$. No associations were found with waist/hip ratio, suicide attempts, renal and gastrointestinal disorders or malignancy (except females with age at diagnosis 1.04 (1.01–1.08), $P=0.0057$) (not shown).
*Except the DSD.
CV, cardiovascular; OR, odds ratio.

at diagnosis of DSD and age at inclusion in the study, but this could only explain a third of the increased risks. A late diagnosis could perhaps be explained by some presenting with their complications and the DSD diagnosis was made simultaneously. The increased risk of different comorbidities with age at diagnosis persisted, however, mostly non-significant when analyzed in the subgroups probably due to the smaller number of individuals. To be diagnosed as early as possible is important in order for management and information to be commenced promptly. This may reduce the risk of future comorbidities. Neonatal screening has already been implemented for CAH in many countries (29) and has been suggested for KS (7). Future studies have to explore if more diagnoses should be included into the neonatal screening programs.

This study has several limitations. Even though we were able to recruit a large number of participants, most were individuals with TS, KS or CAH while it was more difficult to include participants with XY-DSD conditions, partly because those conditions are rarer. There may also have been a selection bias since the participating centers represented many of the most specialized ones in Europe. The questionnaires were constructed in such a way that details of the co-morbidities may not have been captured. There was missing data since the participants could choose not to answer a question or do an examination. Controls were not recruited at the participating centers but large control data were obtained from Eurostat and previous published studies with similar ages, however, not exactly the same age, time period and geographical areas. However, the strengths of this study were that we were able to recruit the highest number of individuals with DSD so far, including some rare variants, and many perspectives of health were examined.

In conclusion, general health seemed good overall in individuals with DSD. However, many medical problems were reported, especially in KS, with a clear increased risk for both somatic and psychiatric morbidities in individuals who were diagnosed later. Knowledge on the specific health issues that might occur in the different diagnoses should be included in the patient education programs, especially during transition. The DSD expert centers have to tailor follow-up programs according to the needs of the individuals and the different diagnostic groups. Therefore, lifelong follow-up by multidisciplinary teams is necessary.

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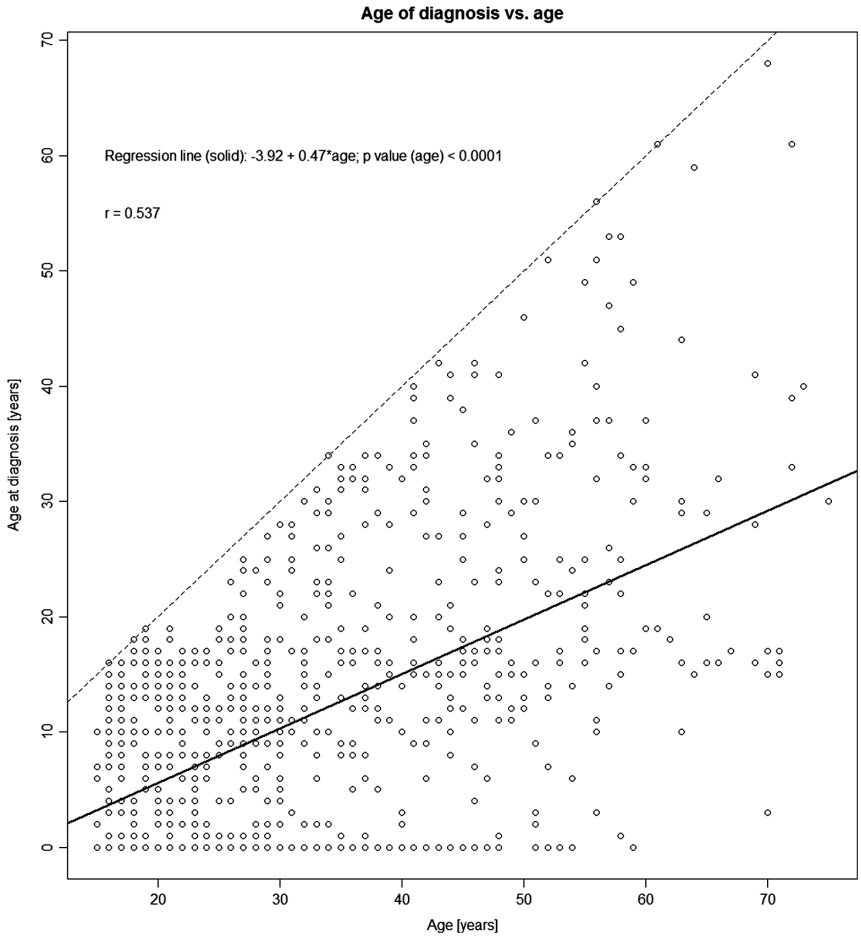

Figure 1
Relationship between age at diagnosis of DSD and age at inclusion in dsd-LIFE study.

Supplementary data
This is linked to the online version of the paper at https://doi.org/10.1530/EC-18-0031.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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