

Clinical Research Article

# Physical and Reported Subjective Health Status in 222 Individuals with XY Disorder of Sex Development

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**Abbreviations:** AD, androgen biosynthesis disorder; BMD, bone mineral density; BMI, body mass index; CAH, congenital adrenal hyperplasia; CAIS, complete androgen insensitivity syndrome; CGD, complete gonadal dysgenesis; DSD, disorders of sex development; HDL, high-density lipoprotein; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; LDL, low-density lipoprotein; PAIS, partial androgen insensitivity syndrome; PGD, partial gonadal dysgenesis.

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## Abstract

**Context:** Little is known about the physical health of individuals with 46,XY disorders of sex development (DSD).

**Objective:** To assess physical and reported subjective health of individuals with XY DSD.

**Methods:** As part of the dsd-LIFE study, patients with an XY DSD condition were analyzed in different diagnosis groups for metabolic parameters, comorbidities, metabolic syndrome, bone outcomes, and reported subjective health. Findings were evaluated by descriptive statistics.

**Results:** A total of 222 patients with XY DSD were included with a mean age of  $28.8 \pm 12.2$  years, mean height of  $175.3 \pm 7.7$  cm, mean weight of  $74.3 \pm 20.0$  kg, and mean body mass index of  $24.1 \pm 6.0$  kg/m<sup>2</sup>. Obesity rate was not increased when descriptively compared with Eurostat data. Fourteen patients had metabolic syndrome (14/175; 8.0%). In

descriptive comparison with data from the DECODE study and World Health Organization, subjects fared better in the categories waist circumference, glucose, triglyceride, cholesterol, and high-density lipoprotein. Of participants with available bone health data, 19/122 (15.6%) patients had a Z-score  $\leq -2.0$  at lumbar spine indicating lowered bone mineral density (BMD). Mostly gonadectomized individuals with complete androgen insensitivity syndrome (CAIS) and no estrogen therapy had lowered BMD at lumbar spine. Individuals with XY DSD performed poorly in the category subjective health in descriptive comparison with Eurostat data.

**Conclusion:** Participants reported a lower subjective health status than Eurostat data but their overall metabolic health status was good. Decreased BMD at lumbar spine was especially present in gonadectomized individuals with CAIS and no estrogen therapy.

**Key Words:** XY DSD, physical and subjective health, bone health, metabolism, comorbidities

The term disorders of sex development (DSD) summarizes different congenital conditions, which are defined through atypical chromosomal, gonadal, or phenotypic sex [1, 2]. The conditions are further classified into (1) sex chromosome DSD, (2) 46,XY DSD, and (3) 46,XX DSD [1, 2]. In detail, sex chromosome DSD includes Turner and Klinefelter syndrome as well as 45,X/46,XY or 46,XX/46,XY chimeric conditions. The 46,XY DSD is a group which encompasses conditions such as complete gonadal dysgenesis (CGD), partial gonadal dysgenesis (PGD), ovotesticular DSD, complete/partial androgen insensitivity syndrome (CAIS/PAIS), enzymatic androgen biosynthesis disorders (ADs), and hypospadias [1, 2]. Moreover, the 46,XX DSD includes mainly persons with XX gonadal dysgenesis, congenital adrenal hyperplasia (CAH), and uterine/vaginal anomalies [1, 2].

Individuals with XY DSD are characterized by a 46,XY karyotype and congenital sex steroid deficiency or action to varying degrees. Most individuals with XY DSD display an impairment of gonadal function while some have additional adrenal impairment. Each specific disorder includes individual health risks and requires individualized treatment strategies. In detail, individuals with CGD display streak gonads without the ability to produce any sex steroids [3]. Furthermore, their streak gonads could develop gonadal tumors and should be removed during childhood [3, 4]. Other DSD conditions such as ovotesticular individuals are characterized by having both ovarian and testicular gonadal tissue [5]. Individuals with CAIS appear phenotypically female, but have male gonads and no Müllerian structures [6]. In CAIS, gonadectomy is recommended after puberty, as the malignancy risk before late puberty is considered very low [7]. Individuals with PAIS and AD present with male, ambiguous, or female external genitalia, depending on the remaining androgen action [8].

Earlier studies have analyzed and described physical comorbidities in patients with other forms of DSD such as Turner syndrome, Klinefelter syndrome, or CAH [9-11]. In a previous dsd-LIFE study, good general health of all

dsd-LIFE participants was reported [12]. However, mental health problems were more prevalent in individuals with DSD, as seen in a prior analysis [13]. Another dsd-LIFE study revealed the correlation between glucocorticoid dose and bone mineral density (BMD) in individuals with CAH [14]. The hormone therapy of the whole dsd-LIFE cohort was previously analyzed and revealed good adherence to therapy in general [15]. In addition, data from the international DSD (I-DSD) registry showed a higher prevalence of being small for gestational age among individuals with XY DSD [16-18]. However, long-term health status of each specific XY DSD condition is mostly unknown. Hormone deficiency and its consequences on bone health in CAIS is well recognized, showing that individuals with CAIS have lower BMD, which may predispose to a higher risk of osteoporosis [19-22]. Gonadectomized individuals with CAIS had low BMD at the lumbar spine and femoral neck [23], whereas hormone replacement therapy improved BMD in subjects with CAIS [23]. In Turner syndrome, early introduction of hormone replacement therapy was associated with better BMD [24]. Another study of individuals with CAIS showed a higher prevalence of obesity as well as increased total cholesterol, low-density lipoprotein (LDL) cholesterol and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) levels [25]. In contrast, for other DSD entities including XY gonadal dysgenesis, PAIS, AD, and hypospadias, data on metabolic and bone health are rare.

To identify physical comorbidities and health risks, we have analyzed metabolic parameters such as metabolic syndrome and bone health of the so far largest cohort of adolescents and adults with XY DSD conditions completed by an evaluation of their reported subjective health status.

## Patients and Methods

### Setting and Registry

This study is part of the European multidisciplinary clinical outcome study dsd-LIFE, including 1040 participants

with DSD conditions recruited and examined across 14 study centers in 6 European countries (France, Germany, The Netherlands, Poland, Sweden, and the UK) [26]. Not all parameters were available of all participants with DSD. The description of results always includes the number of participants with available data. Further details on the study procedures and the participant characteristics are given in the previously published study protocol [26].

### Description of Participants

We report here in detail on the 222 predominantly adult individuals with 46,XY DSD (Table 1). In the present study, this heterogeneous group was divided into 6 subgroups with complete and partial absence of gonadal androgen synthesis or androgen action: CGD  $n = 21$ , PGD (including 5 subjects with ovotesticular DSD)  $n = 42$ , CAIS  $n = 71$ , PAIS  $n = 35$ , AD  $n = 18$ , and Others  $n = 35$ . The subgroup of individuals with AD consists of subjects with 17 $\beta$ -hydroxysteroiddehydrogenase deficiency ( $n = 11$ ), 3 $\beta$ -hydroxysteroiddehydrogenase deficiency ( $n = 2$ ), 5 $\alpha$ -reductase deficiency ( $n = 4$ ), and 17 $\alpha$ -hydroxylase/17,20-lyase defect ( $n = 1$ ). The subgroup Others is composed of subjects with hypospadias ( $n = 25$ ), unknown genital defects ( $n = 7$ ), unknown steroid synthesis defects ( $n = 2$ ), and micropenis ( $n = 1$ ).

A molecular genetic diagnosis was known in 11/21 (52.4%) CGD, 9/42 (21.4%) PGD, 50/71 (70.4%) CAIS, 18/35 (51.4%) PAIS, and 17/18 (94.4%) AD individuals [26]. All subjects of the subgroup Others were solely clinically diagnosed [26].

### Clinical Data

Clinical data were acquired through physical examination (including height, weight, body mass index [BMI], waist and hip circumference, blood pressure), medical history, and questionnaires concerning patient reported outcomes, comorbidities, and current hormone therapy [26]. The medical interviews and physical examination were recorded in case report form. The data were gathered anonymously in a database and evaluated [26]. Blood values were gathered through a fasting blood sample [26].

Metabolic syndrome was defined in accordance with the interdisciplinary joint interim statement of 6 well-recognized institutions (International Diabetes Federation [IDF]; National Heart, Lung, and Blood Institute [NHLBI]; American Heart Association [AHA]; World Heart Federation [WHF]; International Atherosclerosis Society [IAS]; International Association for the Study of Obesity [IASO]) [27]. Any 3 of the following criteria had to be applicable in

order to fulfill the above-mentioned definition of the metabolic syndrome: Population-/country-specific elevated waist circumference (we used the cut-points proposed by the IDF for people of European origin:  $\geq 94$  cm in males and  $\geq 80$  cm in females [28]), triglycerides  $\geq 150$  mg/dL ( $\triangleq 1.7$  mmol/L) or medication for elevated triglycerides, high-density lipoprotein (HDL)-cholesterol  $< 40$  mg/dL ( $\triangleq 1.0$  mmol/L) in males and  $< 50$  mg/dL ( $\triangleq 1.3$  mmol/L) in females or medication for reduced HDL, blood pressure  $\geq 130$  mmHg systolic, and/or 85 mmHg diastolic or antihypertensive medication, fasting glucose  $\geq 100$  mg/dL ( $\triangleq 5.6$  mmol/L), or medication for elevated glucose [27]. The reference range of the reported gender identity was applied while screening for metabolic syndrome. If a participant neither identified as male or female ( $n = 7$ ), the mean of the male and female value for waist circumference ( $\geq 87$  cm) and HDL ( $< 1.15$  mmol/L) was applied. A HOMA-IR  $\geq 2$  was defined as a sign for insulin resistance. The BMI was further divided into categories: underweight (BMI  $< 18.5$  kg/m<sup>2</sup>), normal weight (BMI  $\geq 18.5 < 25$  kg/m<sup>2</sup>), overweight (BMI  $\geq 25 < 30$  kg/m<sup>2</sup>), and obese (BMI  $\geq 30$  kg/m<sup>2</sup>). Regarding remaining clinical and laboratory data, thresholds from the metabolic syndrome definition [27, 28], European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines [29], World Health Organization (WHO) operated Global Health Workforce Statistics [30] and laboratory-specific assessments were used. Metabolic parameters were descriptively compared with data from the WHO [30] and DECODE study [31].

Bone health was evaluated mainly through BMD values. We obtained BMD of the femoral neck and lumbar spine. Dual energy x-ray absorptiometry devices used in different centers were from GE Healthcare (eg, GE-DEXA, Lunar prodigy Densitometer, GE Lunar Prodigy Advance) and Hologic (eg, Hologic Discovery A). Z-score and T-score were calculated and analyzed according to age. Bone health of subjects aged 50 years and older were evaluated for osteopenia and osteoporosis using the T-score as proposed by the WHO [32]. The Z-score was used, as proposed by the International Society for Clinical Densitometry, in subjects younger than 50 years old to assess their bone health [33, 34]. Vitamin D insufficiency ( $\geq 30$  nmol/L and  $< 50$  nmol/L) and deficiency ( $< 30$  nmol/L) was defined according to cut-off values proposed by the Institute of Medicine [35].

### Patient-reported Subjective Health Status

Subjective health was acquired using the general questions: “How is your health in general?” “Would you say it is (very) bad/fair/(very) good?” and “Do you have any longstanding illness or health problem (apart from your condition)?”—with focus on physical, mental, or mixed health problems in the answers. Long-standing limitation was measured by

Table 1. Patient characteristics

	XY DSD (n = 222)	CGD (n = 21)	PGD <sup>a</sup> (n = 42)	CAIS (n = 71)	PAIS (n = 35)	AD <sup>b</sup> (n = 18)	Others <sup>c</sup> (n = 35)	Eurostat <sup>d</sup> % (min-max)
<b>Gender identity—n (%)</b>								
Female	142/222 (64.0*)	20/21 (95.2)	15/42 (35.7)	69/71 (97.2)	17/35 (48.6)	13/18 (72.2)	8/35 (22.9)	
Male	73/222 (32.9*)	0/21	27/42 (64.3)	0/71	18/35 (51.4)	2/18 (11.1)	26/35 (74.3)	
Other	7/222 (3.2*)	1/21 (4.8)	0/42	2/71 (2.8)	0/35	3/18 (16.7)	1/35 (2.9)	
Age years—Mean ± SD (n)	28.8* ± 12.2* (222)	27.4 ± 11.6 (21)	23.6 ± 7.6 (42)	34.6 ± 13.7 (71)	26.8 ± 10.8 (35)	29.7 ± 14.3 (18)	25.6 ± 10.0 (35)	
Height cm—Mean ± SD (n)	175.3 ± 7.7 (205)	177 ± 9.1 (19)	174.6 ± 7.7 (41)	174.3 ± 6.3 (65)	177.1 ± 8.5 (33)	173.3 ± 9.8 (18)	176.4 ± 6.8 (29)	
Weight kg—Mean ± SD (n)	74.3 ± 20.0 (206)	72.9 ± 25.9 (20)	73.3 ± 15.4 (41)	74.4 ± 22.3 (65)	77.2 ± 20.9 (33)	73 ± 18.0 (18)	74.2 ± 17.7 (29)	
BMI kg/m <sup>2</sup> —Mean ± SD (n)	24.1* ± 6.0* (205)	23.2 ± 7.4 (19)	24 ± 4.7 (41)	24.4 ± 6.5 (65)	24.6 ± 6.7 (33)	24.3 ± 5.7 (18)	23.8 ± 5.3 (29)	
BMI—n (%)								
BMI < 18.5	17/205 (8.3)	6/19 (31.6)	2/41 (4.9)	5/65 (7.7)	0/33	1/18 (5.6)	3/29 (10.3)	2.7-5.0
BMI ≥ 18.5-25	122/205 (59.5)	8/19 (42.1)	24/41 (58.5)	39/65 (60.0)	25/33 (75.8)	10/18 (55.6)	16/29 (55.2)	49.3-59.8
BMI ≥ 25-30	42/205 (20.5*)	3/19 (15.8)	11/41 (26.8)	13/65 (20.0)	5/33 (15.2)	4/18 (22.2)	6/29 (20.7)	25.1-30.6
BMI ≥ 30	24/205 (11.7*)	2/19 (10.5)	4/41 (9.8)	8/65 (12.3)	3/33 (9.1)	3/18 (16.7)	4/29 (13.8)	9.6-17.0
<b>Hormone therapy<sup>e</sup>—n (%)</b>								
testosterone	27/215 (12.6)	1/20 (5.0)	12/42 (28.6)	8/66 (12.1)	2/34 (5.9)	2/18 (11.1)	2/35 (5.7)	
estradiol(-valerate)	73/215 (34.0)	8/20 (40.0)	7/42 (16.7)	33/66 (50.0)	8/34 (23.5)	10/18 (55.6)	7/35 (20.0)	
ethinylestradiol	2/215 (0.9)	0/20	0/42	1/66 (1.5)	0/34	0/18	1/35 (2.9)	
estradiol(-valerate) + progestin	21/215 (9.8)	5/20 (25.0)	3/42 (7.1)	7/66 (10.6)	3/34 (8.8)	3/18 (16.7)	0/35	
ethinylestradiol + progestin	9/215 (4.2)	2/20 (10.0)	4/42 (9.5)	3/66 (4.5)	0/34	0/18	0/35	
No hormone replacement	87/215 (40.5)	4/20 (20.0)	17/42 (40.5)	16/66 (24.2)	21/34 (61.8)	4/18 (22.2)	25/35 (71.4)	
<b>Gonadectomy—n (%)</b>								
Yes	160/222 (72.1)	19/21 (90.5)	36/42 (85.7)	62/71 (87.3)	15/35 (42.9)	16/18 (88.9)	12/35 (34.3)	
No	46/222 (20.7)	0/21	6/42 (14.3)	0/71	16/35 (45.7)	1/18 (5.6)	23/35 (65.7)	
Unknown <sup>f</sup>	16/222 (7.2)	2/21 (9.5)	0/42	9/71 (12.7)	4/35 (11.4)	1/18 (5.6)	0/35	

The percentage refers to the number of subjects who answered the specific question.

Abbreviations: DSD, disorder/difference of sex development; CGD/PGD, complete/partial gonadal dysgenesis; CAIS/PAIS, complete/partial androgen insensitivity syndrome; AD, androgen biosynthesis disorders; BMI, body mass index.

<sup>a</sup>Including XY ovotesticular DSD (n = 5). <sup>b</sup>17β-hydroxysteroid dehydrogenase deficiency (n = 11), 3β-hydroxysteroid dehydrogenase deficiency (n = 2), 5α-reductase deficiency (n = 4) and 17α-hydroxylase/17,20 lyase defect (n = 1). <sup>c</sup>Hypospadias (n = 25), unknown defect (n = 7), unknown steroid synthesis defect (n = 2) and micropenis (n = 1). <sup>d</sup>Eurostat database (<http://ec.europa.eu/eurostat/web/health/overview>; last date accessed April 11, 2020). Parameters: year 2014, total sex, age 18-44 year, Germany, France, The Netherlands, Poland, Sweden, UK. <sup>e</sup>For this question multiple answers were possible, as some subjects take more than 1 hormone. Several percentages do not add up to 100%, because the number of answerers were used for calculation of percentage, not the overall number of answers. <sup>f</sup>Six individuals with CAIS had luteinizing hormone, follicle-stimulating hormone values near a range assuming sufficient hormone production without external hormone therapy indicating intact gonads.

\*These values/percentages have been previously published by Falhammar et al.[12].

the question: “For at least the past 6 months, to what extent have you been limited because of a health problem in activities people usually do?” “Would you say you have been severely limited/limited but not severely/not limited at all?” ([www.europeansocialsurvey.org/](http://www.europeansocialsurvey.org/), round 6, 2012). For all XY DSD subgroups, the absolute numbers and percentages of the answers to the above-mentioned questions were calculated, tested for significance between the subgroups, and compared with Eurostat data (<http://ec.europa.eu/eurostat/web/health/overview>; last date accessed April 11, 2020).

## Statistical Analysis

Data are presented in either absolute number with percentages (categorical parameters) or mean value with standard deviation (continuous parameters). All percentages refer to the number of subjects with available data. The results from patient reported subjective health were tested between XY DSD subgroups using Fisher’s exact test.  $P < .05$  was considered to indicate statistical significance, although due to the nature of the study all results are to be interpreted as exploratory.

Where applicable, our results were descriptively compared with data from the WHO [30], the findings from the DECODE study [31] and the Eurostat database (<http://ec.europa.eu/eurostat/web/health/overview>; last date accessed April, 11 2020). Eurostat parameters used for sample creation were year 2018 for subjective health (year 2014 for BMI and comorbidities), both sexes, individuals aged 16-44 years old (18-44 years for BMI, 15-44 years for comorbidities) from Germany, France, The Netherlands, Poland, Sweden, and the UK. WHO database [30] (last date accessed May 29, 2020) parameters used were year 2014 for raised blood glucose, year 2008 for raised cholesterol, both sexes, individuals aged 18+ years (25+ years for cholesterol) from the same above-mentioned 6 countries. Within the DECODE study the prevalence of the metabolic syndrome based on data from 9 European cohorts was analyzed with an almost identical definition as ours [31]. Their resulting metabolic values possessed the same threshold as some of our investigated metabolic parameters. In case of congruence of the thresholds, a descriptive comparison of our findings to their results was done. Analysis was performed using IBM SPSS Statistics software version 24 and R version 3.4.0. [36].

## Ethics

The study was approved by the local Ethics Review Board at each of the 14 study centers and informed consent of the participants was obtained [26].

## Results

### Cohort Characteristics

General characteristics of the 222 individuals with XY DSD and 6 subgroups (CGD; PGD; CAIS, PAIS, AD, Others) are shown in Table 1.

In total, 142 (64.0%) participants identified as females, 73 (32.9%) as males, and 7 (3.2%) individuals reported their gender identity as neither female or male. These percentages were previously published by Falhammar et al. [12]. Almost all subjects in the CGD (20/21; 95.2%), CAIS (69/71; 97.2%) and AD (13/18; 72.2%) subgroup identified as female. Individuals of the Other subgroup identified most often as male (26/35; 74.3%), and the PGD and PAIS subgroups were mixed. Mean age ranged from 34.6 years (SD 13.7) in subjects with CAIS to 23.6 years (SD 7.6) in subjects with PGD, while 17 participants were older than 50 years. Mean height (174-177 cm), mean weight (73-77 kg), and mean BMI (23-25 kg/m<sup>2</sup>) were similar among all groups. The prevalence of overweight individuals (BMI  $\geq 25$ – $<30$  kg/m<sup>2</sup>) ranged from 15.2% to 26.8% and for obese individuals (BMI  $\geq 30$  kg/m<sup>2</sup>) from 9.1% to 16.7% between the subgroups. Less than 10% of all examined individuals were underweight (17/205; 8.3%). The CGD subgroup accounted for most of the underweight (6/17; 35.3%) and the CAIS subgroup for most of the overweight (13/42; 31.0%) and obese (8/24; 33.3%) individuals.

Regarding hormone replacement therapy, the subjects of this study reported taking the following sex steroids: testosterone, estradiol(-valerate), ethinylestradiol, estradiol(-valerate) and progestin, ethinylestradiol and progestin. Usually, people with a female gender identity took estrogen (estradiol, ethinylestradiol, estradiolvalerate with or without progestin) and people with male gender identity testosterone when needed. As expected, most participants on sex steroids took them according to their reported gender identity, except of 10 individuals: Eight subjects with CAIS who identified as female were on testosterone medication. One subject of the PGD and AD subgroup each identified as female and took testosterone in addition to estrogen.

Concerning gonadectomy, almost all subjects of the CGD (19/21; 90.5%), PGD (36/42; 85.7%), CAIS (62/71; 87.3%) and AD (16/18; 88.9%) subgroup had undergone a gonadectomy. In the PAIS subgroup about half reported a gonadectomy (15/35; 42.9%) and half negated one (16/35; 45.7%), while most of the individuals in the Others subgroup did not have a gonadectomy (23/35; 65.7%, Table 1).

Nine subjects with CAIS had no information concerning gonadectomy surgery. However, out of those 9 cases, 7 had no hormonal replacement. From 6 out of these 7 cases

luteinizing hormone and follicle-stimulating hormone values were available and in or near a range, assuming/suggesting a sufficient hormone production of intact gonads. Therefore, in total 6 individuals with CAIS were identified to having intact gonads.

## Metabolism

Metabolic parameters analyzed are shown in [Table 2](#). Increased cholesterol was found in 37.9% (67/177) and increased LDL cholesterol in 28.5% (49/172) of all cases. Hypercholesterolemia with total cholesterol peaked in CAIS (31/53; 58.5%) and for LDL hypercholesterolemia in PGD (12/34; 35.3%). The waist circumference was elevated in 38.9% of patients who identified as females (35/90), in 21.6% (11/51) of participants who identified as males, and in 50% (1/2) of those identifying as other gender. Fasting blood glucose  $\geq 5.6$  mmol/L could be identified in 12.9% (20/155) and  $\geq 7.0$  mmol/L in 2.6% (4/155) of all participants. A triglyceride value  $\geq 1.7$  mmol/L was present in 11.4% (20/175) of the subjects. The mean HOMA-IR was 2.3 (SD 1.7) ranging from 2 in CAIS to 2.6 in PAIS.

In 14 individuals, criteria for metabolic syndrome were fulfilled (14/175; 8.0%). Only 1 subject with metabolic syndrome reported taking antidiabetic, antihypertensive, and lipid-lowering medication. In total, 8 individuals with metabolic syndrome identified as females and 6 reported themselves as males. The 8 females consisted of patients with CAIS ( $n = 4$ ), PAIS ( $n = 2$ ), CGD ( $n = 1$ ), and AD ( $n = 1$ ). In 6/8 (75.0%) of reported females an estrogen hormone replacement therapy (estradiol or estradiol valerate) was given, while the other 2 were individuals with PAIS without any hormone replacement therapy. All 8 females with metabolic syndrome had undergone a gonadectomy. The 6 males with metabolic syndrome consisted of patients with hypospadias ( $n = 4$ ), micropenis ( $n = 1$ ), and PGD ( $n = 1$ ). The individual with PGD was the only one on hormone replacement therapy (testosterone) and had a gonadectomy. The remaining males with metabolic syndrome (5/6; 83.3%) still had their gonads.

## Bone Health

All parameters on bone health and number of included participants with assessed data are shown in [Table 3](#). In individuals with XY DSD <50 years, a Z-score  $\leq -2.0$  at the femoral neck was seen in 3/100 (3.0%) and at lumbar spine in 19/122 (15.6%). Almost all subjects with Z-score  $\leq -2.0$  at the femoral neck (2/3; 66.7%) or respectively at the lumbar spine (16/19; 84.2%) had a gonadectomy. In participants aged 50 years and older, a T-score  $\leq -2.5$  at the femoral neck was found in 1/9 (11.1%) and at the lumbar

spine in 4/13 (30.8%). All subjects with T-score  $\leq -2.5$  reported of a gonadectomy.

## Analysis of different subgroups

**CAIS.** More than half (10/19; 52.6%) of those with reduced Z-score at lumbar spine had CAIS of which almost all identified as female (9/10; 90.0%). Of these 10 individuals, 3 were on estrogen, 4 on solely testosterone, and 3 were without hormone supplementation. Nine out of 10 (90.0%) of these individuals had a gonadectomy. At the femoral neck, no individual with CAIS on hormone medication showed a Z-score  $\leq -2.0$ , but there were 2 subjects (1 with gonads and 1 without) with decreased Z-score at the femoral neck without having any hormone medication. Concerning the T-score, 1 individual with CAIS without gonads and without hormone replacement therapy had a T-score  $\leq -2.5$  at lumbar spine while none had a T-score  $\leq -2.5$  at the femoral neck.

Six individuals with CAIS had sufficient gonadal hormone production. Out of these 6, 2 had a below normal Z- or T-score, of which 1 ( $\geq 50$  years) additionally reported of a fracture.

Eight individuals with CAIS were on testosterone replacement therapy after gonadectomy, of which half (4/8; 50.0%) had a Z-score  $\leq -2.0$  at lumbar spine and none reported of a fracture.

**PGD.** No individual with examined BMD had a Z-score  $\leq -2.0$ . There was no subject in the PGD subgroup  $\geq 50$  years.

**CGD, PAIS, AD, Others.** In all of these subgroups occasional cases of subjects with decreased Z-score or respectively T-score were found: 1 individual from the Others subgroup without gonads and on estrogen had a decreased Z-score at the femoral neck. Nine individuals had a decreased Z-score at the lumbar spine: 1 subject with CGD with an unknown gonadal status and without hormone supplementation; 3 individuals with PAIS without gonads but 2 of them with estrogen- and the other 1 without hormone replacement therapy; 4 subjects (AD) without gonads but 1 was on estrogen, 1 on estrogen and testosterone, 1 solely on testosterone, and 1 without hormone supplementation; and finally 1 individual from the Others group with gonads and without hormone replacement therapy. Regarding T-score, 1 subject (CGD) had a T-score  $\leq -2.5$  at the femoral neck and lumbar spine, and 2 solely at the lumbar spine (1 individual with PAIS and 1 from Others). All subjects with T-score  $\leq -2.5$  had a gonadectomy. The only subject with T-score  $\leq -2.5$  and hormone therapy (estrogen) was found in the Others subgroup. All the remaining individuals with T-score  $\leq -2.5$  had no hormone therapy.

Regarding fractures, 25/204 (12.3%; percentage previously published by Falhammar et al. [12]) of the individuals with XY DSD reported of a fracture. Almost all of

**Table 2. Metabolic parameters of the XY DSD cohort**

	XY DSD (n = 222)	CGD (n = 21)	PGD (n = 42)	CAIS (n = 71)	PAIS (n = 35)	AD (n = 18)	Others (n = 35)	Reference value <sup>e</sup> %
<b>WC female<sup>a</sup>—n (%)</b>								
Female ≥ 80 cm	35/90 (38.9)	3/11 (27.3)	4/8 (50.0)	19/46 (41.3)	3/13 (23.1)	3/5 (60.0)	3/7 (42.9)	59.5
<b>WC male<sup>a</sup>—n (%)</b>								
Male ≥ 94 cm	11/51 (21.6)	0/0	4/25 (16.0)	0/0	1/12 (8.3)	1/1 (100.0)	5/13 (38.5)	50.4
<b>WC other<sup>b</sup>—n (%)</b>								
Other ≥ 87 cm	1/2 (50.0)	0/0	0/0	0/1	0/0	0/0	1/1 (100.0)	
<b>RRsys mmHg—Mean ± SD (n)</b>	123.3 ± 14.9(171)	123.7 ± 15.5(17)	126.4 ± 12.1(37)	122 ± 17.6(49)	120 ± 14.8 (30)	126.1 ± 12.4(15)	123.3 ± 14.4(23)	
<b>RRdia mmHg—Mean ± SD (n)</b>	74.9 ± 10.9(171)	74.5 ± 11.3(17)	75.5 ± 10.3(37)	75.9 ± 9.6(49)	74.1 ± 10.4(30)	74.1 ± 10.2(15)	73.8 ± 15.4(23)	
<b>HOMA-IR—mean ± SD (n)</b>	2.3 ± 1.7 (134)	2.4 ± 1.7 (14)	2.5 ± 1.8 (32)	2 ± 1.7 (34)	2.6 ± 1.8 (22)	2 ± 2.4 (11)	2.1 ± 1.0 (21)	
<b>Glucose—n (%)</b>								
≥5.6 mmol/L	20/155 (12.9)	1/16 (6.3)	1/34 (2.9)	7/41 (17.1)	2/27 (7.4)	4/12 (33.3)	5/25 (20.0)	31.8-44.9
≥7.0 mmol/L	4/155 (2.6)	0/16	0/34	1/41 (2.4)	1/27 (3.7)	0/12	2/25 (8.0)	4.3-7.7 <sup>d</sup>
<b>Insulin—n (%)</b>								
Over normal limit	9/151 (6.0)	1/16 (6.3)	2/33 (6.1)	4/44 (9.1)	1/25 (4.0)	1/12 (8.3)	0/21	
<b>Cholesterol—n (%)</b>								
≥5.0 mmol/L	67/177 (37.9)	5/18 (27.8)	12/36 (33.3)	31/53 (58.5)	8/31 (25.8)	4/14 (28.6)	7/25 (28.0)	51.8-65.6 <sup>d</sup>
<b>Triglyceride—n (%)</b>								
≥1.7 mmol/L	20/175 (11.4)	3/18 (16.7)	2/36 (5.6)	7/52 (13.5)	2/31 (6.7)	0/14	6/24 (25.0)	23.8-36.4
<b>LDL—n (%)</b>								
≥3.0 mmol/L	49/172 (28.5)	5/17 (29.4)	12/34 (35.3)	15/53 (28.3)	7/29 (24.1)	2/14 (14.3)	8/25 (32.0)	
<b>HDL—n (%)</b>								
<1.0 mmol/L (male)	5/171 (2.9)	0/17	1/34 (2.9)	0/53	0/28	0/14	4/25 (16.0)	27.3
<1.3 mmol/L (female)	9/171 (5.3)	2/17 (11.8)	0/34	3/53 (5.7)	3/28 (10.7)	0/14	1/25 (4.0)	29.0

The percentage refers to the number of subjects who answered the specific question.

Abbreviations: WC, waist circumference; RR, blood pressure; sys, systolic; dia, diastolic; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; LDL/HDL, low-/high-density lipoprotein.

<sup>a</sup>Female or male gender identity. <sup>b</sup>Mean of the female and male value was used. <sup>c</sup>Unless noted otherwise, all reference values are from a study publicized by Q. Qiao and the DECODE study group [31]. <sup>d</sup>These values are from Global Health Workforce statistics [30] (last date accessed May 29 2020). Parameters: year 2014 for glucose (year 2008 for cholesterol), both sexes, individuals aged 18+ years (2.5+ years for cholesterol).

**Table 3.** Bone parameters of the XY DSD cohort

	XY DSD (n = 222)	CGD (n = 21)	PGD (n = 42)	CAIS (n = 71)	PAIS (n = 35)	AD (n = 18)	Others (n = 35)
<b>Femoral neck (age &lt; 50 years)—n (%)</b>							
Z-score > -2.0	97/100 (97.0)	7/7 (100)	30/30 (100)	26/28 (92.9)	15/15 (100)	8/8 (100)	11/12 (91.7)
Z-score ≤ -2.0	3/100 (3.0)	0/7	0/30	2/28 (7.1)	0/15	0/8	1/12 (8.3)
<b>Lumbar spine (age &lt; 50 years)—n (%)</b>							
Z-score > -2.0	103/122 (84.4)	9/10 (90.0)	31/31 (100)	21/31 (67.7)	19/22 (86.4)	6/10 (60.0)	17/18 (94.4)
Z-score ≤ -2.0	19/122 (15.6)	1/10 (10.0)	0/31	10/31 (32.3)	3/22 (13.6)	4/10 (40.0)	1/18 (5.6)
<b>Femoral neck (age ≥ 50 years)—n (%)</b>							
T-score ≥ -1	2/9 (22.2)	0/1	0/0	2/4 (50.0)	0/1	0/2	0/1
T-score > -2.5 and < -1	6/9 (66.7)	0/1	0/0	2/4 (50.0)	1/1 (100)	2/2 (100)	1/1 (100)
T-score ≤ -2.5	1/9 (11.1)	1/1 (100)	0/0	0/4	0/1	0/2	0/1
<b>Lumbar spine (age ≥ 50 years)—n (%)</b>							
T-score ≥ -1	4/13 (30.8)	0/1	0/0	3/6 (50.0)	0/2	0/2	1/2 (50.0)
T-score > -2.5 and < -1	5/13 (38.5)	0/1	0/0	2/6 (33.3)	1/2 (50.0)	2/2 (100)	0/2
T-score ≤ -2.5	4/13 (30.8)	1/1 (100)	0/0	1/6 (16.7)	1/2 (50.0)	0/2	1/2 (50.0)
<b>25 OH-Vitamin D3—n (%)</b>							
Sufficient (≥50 nmol/L)	91/156 (58.3)	7/14 (50.0)	25/33 (75.8)	27/47 (57.4)	11/27 (40.7)	9/13 (69.2)	12/22 (54.5)
Insufficient (≥30 nmol/L < 50 nmol/L)	34/156 (21.8)	2/14 (14.3)	5/33 (15.2)	11/47 (23.4)	10/27 (37.0)	1/13 (7.7)	5/22 (22.7)
Deficient (<30 nmol/L)	31/156 (19.9)	5/14 (35.7)	3/33 (9.1)	9/47 (19.1)	6/27 (22.2)	3/13 (23.1)	5/22 (22.7)
<b>Osteoporosis—n (%)</b>							
gonadectomized	17/204 (8.3*)	2/19 (10.5)	0/41	11/66 (16.7)	1/33 (3.0)	2/18 (11.1)	1/27 (3.7)
no hormone therapy	16/17 (94.1)	2/2 (100)	0/0	10/11 (90.9)	1/1 (100)	2/2 (100)	1/1 (100)
<b>Fractures—n (%)</b>							
gonadectomized	7/17 (41.2)	1/2 (50.0)	0/0	4/11 (36.4)	1/1 (100)	1/2 (50.0)	0/1
no hormone therapy	25/204 (12.3*)	2/17 (11.8)	1/42 (2.4)	14/65 (21.5)	1/33 (3.0)	2/18 (11.1)	5/29 (17.2)
gonadectomized	22/25 (88.0)	2/2 (100)	1/1 (100)	13/14 (92.9)	1/1 (100)	2/2 (100)	3/5 (60.0)
no hormone therapy	13/25 (52.0)	2/2 (100)	0/1	8/14 (57.1)	0/1	1/2 (50.0)	2/5 (40.0)

The percentage refers to the number of subjects who answered the specific question.

\*These percentages have been previously published by Falhammar et al [12].



those subjects had a gonadectomy (22/25; 88.0%), except of 2 individuals from the Others subgroup and 1 individual with CAIS. About half of the subjects who reported of a fracture were not on hormone replacement therapy (13/25; 52.0%). The remaining subjects were mostly on estrogen (11/25; 44.0%) and 1 individual was on testosterone (1/25; 4.0%).

In total, 14/25 (56.0%) individuals with XY DSD and self-reported fracture had available BMD values. Out of these individuals 8/14 (57.1%) had a Z-score  $\leq -2.0$  or respectively T-score  $< -1$  at the lumbar spine or femoral neck. Almost all of them had a gonadectomy (7/8; 87.5%) and more than half were without hormone therapy (5/8; 62.5%). The remaining 3 individuals were on estrogen therapy (3/8; 37.5%). Most of the subjects with Z-score  $\leq -2.0$  or respectively T-score  $< -1$  at the lumbar spine or femoral neck and fracture were individuals with CAIS (6/8; 75.0%).

Osteoporosis was reported by 17/204 (8.3%; percentage previously published by Falhammar et al. [12]) of the participants. Almost all of them were gonadectomized (16/17; 94.1%) and about half were without hormone therapy (7/17; 41.2%). The remaining individuals who reported of osteoporosis were on estrogen (6/17; 35.3%) and testosterone (3/17; 17.6%), and in 1 case hormone therapy was not assessed.

Regarding vitamin D3, almost half (65/156; 41.7%) of all participants had a vitamin D3 insufficiency or vitamin D3 deficiency. Among the 19 subjects with a Z-score  $\leq -2.0$  at lumbar spine, 14 (73.7%) had either vitamin D3 insufficiency or deficiency. The blood values calcium, phosphate, bone alkaline phosphate and osteocalcin were within normal level in the majority of cases.

### Patient Reported Subjective Health Status and Other Comorbidities

The findings of patient reported subjective health are depicted in detail in Table 4. Individuals with CAIS were the most satisfied with 49/70; (70.0%) perceiving their health as “very good or good” while individuals with PAIS were the least satisfied with 7/33 (21.2%) rating their health as “bad or very bad.” However, the differences in overall subjective health between the subgroups did not reach significance ( $P = .66$ ).

The question for a longstanding illness or health problem was affirmed in 19.6% (40/204) for a physical problem, in 3.4% (7/204) for a mental problem and in 7.4% (15/204) for a combination of both health impairments. The individuals of the CGD subgroup stated most to have additional longstanding illness or health problems apart from their underlying condition (11/18, 61.1%). The

lowest percentage (25.8%; 8/31) could be found in the “Others” subgroup. There was no statistical significance in frequency of longstanding illness or health problems between the subgroups ( $P = .21$ ).

When asked about limitation of everyday activities, 132/203 (65.0%) reported “no limitation at all,” 55/203 (27.1%) “limited but not severely,” and 16/203 (7.9%) “severely limited.” In general, individuals with PAIS reported mostly “no limitation at all” (23/29; 79.3%), but also in 13.8% (4/29) to be “severely limited” in everyday activities. Overall, the individuals reporting to be the least limited were subjects with CAIS, only feeling “severely limited” in in 5.8% (4/69). There was no difference in reported limitations in everyday activities between the subgroups ( $P = .26$ ).

Frequency of comorbidities was compared to reference values (Eurostat <http://ec.europa.eu/eurostat/web/health/overview>; last date accessed April 11, 2020) for the diagnoses diabetes mellitus, heart attack, stroke, hypertension, allergies, asthma, renal insufficiency, and urinary incontinence. Most were near or within normal range except of the diagnosis urinary incontinence. Of the whole XY DSD cohort, in 6.5% of the individuals urinary incontinence was reported in contrast to maximum of 2.2% in the reference population (Eurostat <http://ec.europa.eu/eurostat/web/health/overview>; last date accessed April 11, 2020).

### Discussion

This study is the first detailed follow-up study of individuals with rare XY DSD conditions from the dsd-LIFE study. We examined metabolism, bone health, physical comorbidities and patient reported subjective health in different XY DSD conditions.

One of our aims was to evaluate if gonadal/adrenal impairment increases the risk of concomitant metabolic diseases, especially the metabolic syndrome. Regarding body weight (BMI), we found a rate of overweight and obese individuals with XY DSD similar or rather slightly lower than Eurostat data (<http://ec.europa.eu/eurostat/web/health/overview>). Regarding the prevalence of obese individuals, our results (9.1-16.7%) were almost identical to Eurostat data. Therefore, our findings indicate that individuals with XY DSD have no increased risk for obesity. Interestingly, the CGD subgroup harbored a much higher number of individuals with underweight, when descriptively compared to Eurostat data, which warrants further investigation.

Eight individuals with CAIS were on testosterone treatment despite a female gender identity. Testosterone is not the usual regimen for individuals with CAIS and female gender identity, but as seen in a prior study by Birnbaum et al. it is a safe alternative to estrogen therapy and is even beneficial for patients with low sexual desire [37].

**Table 4.** Patient reported subjective health status in the XY DSD cohort compared with the European reference population

	XY DSD (n = 222)	CGD (n = 21)	PGD (n = 42)	CAIS (n = 71)	PAIS (n = 35)	AD (n = 18)	Others (n = 35)	P <sup>a</sup>	Eurostat <sup>c</sup> % (min—max)
<b>How is your health in general?—n (%)</b>									
Very good or good	136/215 (63.3*)	12/21 (57.1)	28/41 (68.3)	49/70 (70.0)	15/33 (45.5)	11/18 (61.1)	21/32 (65.6)	.66	83.4-86.7
Fair	57/215 (26.5*)	6/21 (28.6)	9/41 (22.0)	16/70 (22.9)	11/33 (33.3)	6/18 (33.3)	9/32 (28.1)		11.1-13.3
Bad or very bad	22/215 (10.2*)	3/21 (14.3)	4/41 (9.8)	5/70 (7.1)	7/33 (21.2)	1/18 (5.6)	2/32 (6.3)	.21 <sup>b</sup>	2.2-3.5
<b>Do you have any longstanding illness or health problem? (apart from your condition)—n (%)</b>									
Yes	72/204 (35.3*)	11/18 (61.1)	10/38 (26.3)	23/67 (34.3)	12/32 (37.5)	8/18 (44.4)	8/31 (25.8)		16.9-27.4
Physical problem	40/204 (19.6)	5/18 (27.8)	4/38 (10.5)	17/67 (25.4)	5/32 (15.6)	5/18 (27.8)	4/31 (12.9)		
Mental problem	7/204 (3.4)	3/18 (16.7)	0/38	1/67 (1.5)	2/32 (6.3)	1/18 (5.6)	0/31		
Both	15/204 (7.4)	1/18 (5.6)	3/38 (7.9)	4/67 (6.0)	2/32 (6.3)	1/18 (5.6)	4/31 (12.9)		
No answer	10/204 (4.9)	2/18 (11.1)	3/38 (7.9)	1/67 (1.5)	3/32 (9.4)	1/18 (5.6)	0/31		
No	132/204 (64.7)	7/18 (38.9)	28/38 (73.7)	44/67 (65.7)	20/32 (62.5)	10/18 (55.6)	23/31 (74.2)	.26	
<b>For at least the past 6 months, to what extent have you been limited because of a health problem in activities people usually do?—n (%)</b>									
Severely limited	16/203 (7.9)	2/19 (10.5)	3/38 (7.9)	4/69 (5.8)	4/29 (13.8)	1/17 (5.9)	2/31 (6.5)		2.1-5.8
Limited but not severely	55/203 (27.1)	7/19 (36.8)	8/38 (21.1)	21/69 (30.4)	2/29 (6.9)	8/17 (47.1)	9/31 (29.0)		5.2-16.5
Not limited at all	132/203 (65.0)	10/19 (52.6)	27/38 (71.1)	44/69 (63.8)	23/29 (79.3)	8/17 (47.1)	20/31 (64.5)		80.7-92.7

The percentage refers to the number of subjects who answered the specific question.

<sup>a</sup>The results from subjective health were tested between the subgroups for significance. <sup>b</sup>This P value refers to the question "Do you have any longstanding illness—Yes/No." Eurostat database (<http://ec.europa.eu/eurostat/web/health/overview>; last date accessed April 11, 2020). Parameters: year 2018, total sex, age 16-44 year, Germany, France, the Netherlands, Poland, Sweden, the United Kingdom.

<sup>c</sup>These percentages have been previously published by Falhammar et al. [12].

All XY DSD subgroups had a very slightly elevated HOMA-IR although most individuals with XY DSD had normal glucose and insulin values. The rate of self-reported diabetes was low. A higher prevalence of elevated waist circumference, glucose, cholesterol, triglyceride, and lowered HDL levels were not found in our study. In contrast, descriptively compared with reference data [30, 31], individuals with XY DSD seemed to achieve better results: The calculated percentages were distinctly lower. However, the reference data from the DECODE study publication [31] was based on individuals 30 years and older with a mean age range between 52 and 62 years. The mean age of our study was approximately 29 years. In addition, the cohort of the DECODE study publication [31] consisted of patients from Italy, Finland, The Netherlands, the UK, Poland, and Sweden. Germany and France, from where most our participants come from, were not included. This limits the comparability of the data. Raised cholesterol levels peaked in the CAIS subgroup (58.5%) while the other subgroups achieved results between 25.8% and 33.3%, which warrants further investigations. One can only speculate, why individuals with CAIS had higher cholesterol levels. One study showed a correlation between low testosterone levels and hyperglycemia, hypercholesterolemia, hypertriglyceridemia, and obesity in testicular germ cell tumor survivors [38]. To explore the pathomechanism, further investigations are necessary.

Only a few individuals with XY DSD had metabolic syndrome. However, this may be due the limitation of incomplete reporting of metabolic laboratory data. Furthermore, for the data analysis of the metabolic syndrome, we used female reference ranges and cut-offs when the subject identified as female despite their 46,XY karyotype, based on their phenotypically female appearance. Yet it should be noted that almost all participants who identified as females with metabolic syndrome were on estrogen medication and no individual with CAIS on testosterone medication had metabolic syndrome. Further studies on the influence of hormone replacement therapy in individuals with XY DSD and the risk of metabolic syndrome are needed.

Regarding bone health, reduced Z-scores were found in all XY DSD subgroups except PGD. However, similar population-based studies regarding the prevalence of decreased Z-scores do not exist to our knowledge, so a statement cannot be made whether the rate is increased or not. Moreover, extended studies should be conducted to examine BMD, in relation to hormonal status and other influencing factors. Especially, the timing of gonadectomy and full sex hormone reposition should be taken into account when assessing BMD: The gain of bone mass is dependent on sex steroids and mostly occurs during adolescence [39, 40]. Thus, with the beginning of puberty

adequate sex steroids levels are of particular importance in order to achieve peak bone mass in adulthood [39]. If necessary, the puberty must be inducted through hormone replacement therapy [3]. As optimal timing of pubertal induction currently the mean pubertal age (eg, around 11-12 years in girls) is recommended [41]. Additionally, the time of transition from the pediatric to adult health care is a critical time point when adolescents with chronic diseases often fall out of medical surveillance [42]. This bears the risk of a decreased compliance to hormone therapy, which negatively affects BMD. All those factors should be considered and analyzed when assessing BMD. As timing of gonadectomy and full sex hormone reposition was not collected in the dsd-LIFE study, their influence on BMD could not be assessed. Furthermore, a previous dsd-LIFE study revealed a negative correlation between the glucocorticoid dose during adolescence and BMD in adulthood in individuals with CAH [14]. Some subjects of our study reported the use of progestin in addition to estrogen. This could be a further influencing factor as medroxyprogesterone acetate is associated with a decrease of BMD [43, 44]. However, estrogen replacement might positively influence the BMD in CAIS, as our subjects on estrogen achieved better BMD in total than subjects with testosterone treatment alone or without any hormone supplementation. Almost all of the subjects with CAIS and decreased BMD at lumbar spine had a gonadectomy which underlines the necessity of care of these patients ensuring an optimal hormone replacement therapy. Our findings further suggest that BMD in these patient groups is more severely impaired at the lumbar spine region than the femoral neck. Hence, examination should also include the lumbar spine region when assessing BMD in individuals with XY DSD. One review [23] suggested that bone health in CAIS and intact gonads is not greatly impaired but still reduced, especially at the lumbar spine. Our findings are in accordance to the above-mentioned review and may suggest that intact gonads reduce but not prevent the general risk of osteoporosis for individuals with CAIS. The number of subjects aged 50 years and older was low (mean age of 28.8 years). Therefore, the BMD could be assessed only from few individuals aged 50 years and older, which is a limitation of this study.

Most of the subjects reporting a fracture or osteoporosis had a gonadectomy and half of them were on no hormone therapy. Thus, the importance of adequate hormone therapy especially after a gonadectomy should be more stressed by the physicians to reduce the risk of osteoporosis and fractures.

Vitamin D3 insufficiency/deficiency may have influenced the development of low BMD in our study population as vitamin D deficiency is associated with accelerated bone loss [45]. A possible contributing factor in this study is the

inclusion of patients of the northern/western and middle Europe where sun exposure is low and blood sampling was performed independent of season.

Regarding subjective health, all XY DSD subgroups reported worse subjective health when descriptively compared with the samples of the general European population. Although it must be noted that the question about health in general in our study combined mental, physical, and social health as 1 item. Thus, no conclusions can be drawn about the specific cause (mental, physical, and/or social health) that contributed to the participants' ratings. However, it is known that individuals with DSD more often have mental health problems than the normal population [46, 47]. This fact was also seen in a previously conducted analysis concerning the mental health of this study population [13]. Therefore, the mental health problems individuals with DSD suffer from must have certainly influenced the participants' ratings. One can speculate, that the individuals with CAIS most reported their health as "very good or good" because of their female appearance since birth, which possibly poses less psychological distress during childhood development than other situations with varying degrees of virilization. This hypothesis may likewise partly explain why many individuals with PAIS reported their subjective health as "bad or very bad." Since PAIS covers all variations between female and male appearance. To verify this hypothesis, the satisfaction rate of individuals with XY DSD with their own appearance is needed, which was not part of this work. However, it must be noted that individuals with CGD also have female appearance since birth but did not reach such a positive rating regarding subjective health as individuals with CAIS. A gonadectomy often influences participants' lives negatively [48], but the rate of gonadectomy was nearly equal in the CGD and CAIS groups. A possible reason for the different rating in general health might be the obvious higher rate of patients with CGD stating to have additional longstanding illness or health problems apart from their underlying condition.

Concerning comorbidities, the rate of reported urinary incontinence was slightly higher than the reference population. The highest percentage (11.3%) was found in the CAIS subgroup. One possible explanation could be the procedures individuals with XY DSD go through (eg, vaginal lengthening, sex reassignment surgery) that may have led to urinary incontinence. To validate this hypothesis a thorough urogenital examination had to be carried out in those who reported urinary incontinence, which was not part of this study.

A major weakness of this study is that the results are mostly descriptive and were descriptively compared, which

limits the conclusions. This descriptive analysis was chosen due the nature of this study: XY DSD diagnoses are very rare. Therefore, cohort sizes do not allow thorough statistical analyses. In addition, there was no proper control group, which should be established for future studies. Nevertheless, even with a descriptive analysis a tendency can be made out. The resulting tendencies are of interest for physicians and may still enhance the care of individuals with XY DSD. Furthermore, the present findings are also useful in guiding future research on XY DSD.

In summary, we analyzed the largest cohort of individuals with XY DSD divided into different subgroups according to diagnosis. Incomplete data sets were a major limitation of the study. Nevertheless, this study describes the overall physical and reported subjective health status of individuals with XY DSD and their specific rare condition. We found good physical health in all XY DSD subgroups: Their obesity rate was similar to the European population. The rate of overweight was even slightly lower. Metabolic parameters were within normal range when descriptively compared with reference values except for a slightly elevated mean HOMA-IR. Only few individuals with XY DSD had metabolic syndrome. The participants of this study were not facing any significant health risks apart from the existence of reduced BMD. However, their reported subjective health was worse than the general population.

In conclusion, the health status of individuals with XY DSD showed good metabolic health, the presence of decreased BMD in at most 15.6% of subjects younger than 50 years, and lower scores of reported subjective health. Therefore, regular screening of bone health values in individuals with XY DSD, especially of gonadectomized individuals with CAIS and no hormone therapy, is recommended. For best possible long-term health, individuals with XY DSD should be encouraged to regularly take their hormone replacement therapy and dietary supplements (eg, vitamin D) if required. To care for individuals with XY DSD is a challenging task, considering the needs and wants of each individual. It should include an interdisciplinary team of endocrinologists, psychologists, and further specialists as necessary.

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**Disclosures:** The authors report no conflicts of interest in this work and have nothing to disclose.

**Data Availability:** The datasets analyzed during the current study are not publicly available as long as primary analyses for other outcomes of dsd-LIFE have not been completed. Thereafter scientific public use files are planned. The first and the corresponding author affirm that the manuscript is an honest, accurate and transparent account of the study being reported; no important aspects of the study have been omitted; and any discrepancies from the study as planned have been explained.

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

**Patient involvement:** Individuals with DSD or their representatives participated in the study design through: work in focus groups for the development of condition-specific self-constructed items, work on the scientific advisory board and recruitment through patient advocacy groups. Representatives of the scientific advisory board were involved throughout study development and data collection.

**Ethics approval and consent to participate:** Ethics approval was obtained as appropriate to each country, eg, Ethics Commission of the Charité Universitätsmedizin; reference number EA2/069/13. We obtained written informed consent from all participants and if the participant was underage, both the participants and the parents in cases of young people aged 16-18 years gave written informed consent.

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