Morbidity, Mortality, and Socioeconomics in Females With 46,XY Disorders of Sex Development: A Nationwide Study

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Context: Little is known about long-term health outcomes in phenotypic females with 46,XY disorders of sex development (XY females), and the socioeconomic profile has not been described in detail.

Objective: To describe morbidity, mortality, and socioeconomic status in XY females in a comparison to the general population.

Design: Nationwide registry study with complete follow-up.

Setting: Uniform public health care system.

Participants: A total of 123 XY females karyotyped in Denmark during 1960 to 2012 and a randomly selected age-matched control cohort of 12,300 females and 12,300 males from the general population.

Main Outcome Measures: Overall mortality and morbidity as well as cause-specific morbidity; medicine use and socioeconomics (education, income, cohabitation, motherhood, and retirement).

Results: Compared with female controls, overall morbidity was increased in XY females [hazard ratio (HR), 1.72; 95% confidence interval (CI), 1.43 to 2.08] but not when excluding diagnoses associated with the specific disorder of sex development (DSD) diagnosis or pregnancy and birth (HR, 1.13; CI, 0.93 to 1.37). Mortality was similar to controls (HR, 0.79; CI, 0.35 to 1.77). Cohabitation (HR, 0.44; CI, 0.33 to 0.58) and motherhood (HR, 0.10; CI, 0.05 to 0.18) were reduced in XY females but education (HR, 0.92; CI, 0.61 to 1.37) was similar to controls. Income was higher than among controls in the older years.

Conclusions: Morbidity was not increased in XY females when excluding diagnoses associated to the DSD condition *per se*. Judged on education and income, XY females perform well in the labor market. However, DSD seems to impact on the prospects of family life. **(*J Clin Endocrinol Metab* 103: 1418–1428, 2018)**

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Abbreviations: AIS, androgen insensitivity syndrome; CAIS, complete androgen insensitivity syndrome; CI, confidence interval; DSD, disorder of sex development; GCT, germ cell tumor; GD, gonadal dysgenesis; HR, hazard ratio; ICD, *International Classification of Diseases*; ICD-8, *International Classification of Diseases*, eighth edition; ICD-10, *International Classification of Diseases*, 10th edition; MSR, Medication Statistics Registry.

The 46,XY disorder of sex development (DSD) affects approximately six phenotypic females per 100,000 newborn girls (we use the term "XY female" here). Androgen insensitivity syndrome (AIS) is most common, followed by gonadal dysgenesis (GD) and disorders of androgen synthesis (1).

Because of the complexity of 46,XY DSD, treatment including sex hormone replacement, genital surgery, and gonadectomy may be required. The DSD condition itself, as well as its treatment, may affect the long-term health outcome in XY females, but the overall knowledge of this association is scarce. However, an increased risk for germ cell tumors (GCTs) is known. GCTs are most prevalent in XY females with GD in whom the prevalence is reported to range between 10% and 60% (2–6). In prepubertal XY females with complete AIS (CAIS) the prevalence has been reported as low as 0.8% to 2% (2, 7), whereas the prevalence of GCTs in postpubertal XY females recently has been reported to 10% (8). The same authors (8) reported an almost similar prevalence (7%) of GCTs in partial AIS, which is considerably lower than previously thought (15% to 50%) (2, 7).

Bone health is another concern in DSD as sex hormones play a pivotal role in bone development and maintenance of bone health (9). Reduced bone mineral density is common in XY females (10–13). Most studies have been conducted in women with CAIS, although, because of endogenous estrogen production in women with AIS who have not undergone gonadectomy, women with GD may be more severely affected (14). Appropriate sex hormone replacement is essential to ensure bone health and prevent osteoporosis in these women.

The DSD diagnosis may carry a stigma because of exposure to many diagnostic procedures and medical follow-up as well as concerns related to fertility, relationships, shame, and the taboo associated with the condition. The latter, however, may have improved during recent years as psychological support and openness have become a more integrated part of clinical management (7, 15) than previously (16).

Other DSD conditions, such as Klinefelter and Turner syndromes, are associated with increased morbidity and mortality due to a wide range of diseases (17, 18). In contrast, we recently reported a similar morbidity in phenotypic males with 46,XX DSD and the general population when we disregarded diagnoses closely associated to the DSD (19). Overall, the socioeconomic profile, when compared with that in the general population, was reduced in all conditions (19–21).

To optimize treatment and care for XY females, broader knowledge of both long-term health outcomes and socioeconomics is essential. Thus, the aim of this study was to examine morbidity, mortality, and socioeconomics (education, cohabitation, motherhood, income, and retirement) in a nationwide cohort of XY females compared with the general population.

Patients and Methods

Setting

Denmark has a uniform public health care system guaranteeing all persons residing in Denmark equal health care access.

The registries

Since 1968, the Danish Civil Registration System has assigned a unique civil personal registration number to all persons residing in Denmark. The civil personal registration number allows accurate matching of data from different data sources.

The Danish National Patient Registry includes data on all somatic inpatient contacts and deaths since 1977. Outpatient contacts as well as psychiatric inpatient and outpatient contacts have been included since 1995. Diagnoses are classified according to the *International Classification of Diseases* [eighth edition (ICD-8) until 1993 and 10th edition (ICD-10) thereafter].

The Medication Statistics Registry (MSR) covers data on all processed medical prescriptions since 1995, including date of processing and Anatomical Therapeutic Chemical Classification System codes. Data do not include medicine use during hospitalization or prescriptions processed by hospital pharmacies.

The Danish Cytogenetic Central Registry contains data on every karyotyping performed in Denmark since 1960.

Statistics Denmark administers an extensive national collection of data collected from around the 1970s and to the present.

Cases and controls

Previously, we identified all officially registered females with a 46,XY karyotype in the Danish Cytogentic Central Registry and their diagnosis was validated by medical record review or by discharge diagnoses from the Danish National Patient Registry. In total, 124 individuals were verified as XY females of whom 123 are included in the present study. Exact diagnosis, age at diagnosis, and other clinical characteristics are provided in Table 1 (1).

The Division of Research Services at Statistics Denmark identified 12,300 female controls and 12,300 male controls (100 females and 100 males per XY female) from the general population matched on age (month and year of birth) (Table 1). All controls were alive on the date of the DSD diagnosis.

Data

Data concerning morbidity (dates of admission and discharge, primary and secondary diagnoses for all inpatient and outpatient contacts), medical prescriptions (date of processing and Anatomical Therapeutic Chemical Classification System code) mortality (date and cause of death), socioeconomic parameters (education, income, retirement owing to sickness or age, cohabitation and children, including adopted children) and dates of emigration were retrieved for all XY females and controls, if relevant (for further details, see the Supplemental Material and Methods).

Table 1. Diagnosis, Year of Birth, Age at Diagnosis, and Gonadectomy in XY Females

Cases (per Diagnosis) and Controls	Participants (n)	Median Year of Birth (Range)	Median Age (Years) at Diagnosis (Range)	Gonadectomy: Yes/No/ Unknown (n)	Median Age (Years) at Gonadectomy (Range)
Cases					
AIS	78	1975 (1917–2012)	7.5 (0.0–34.4)	66/6/6	8.3 (0.6–62.4)
GD	25	1976 (1952–1997)	17.0 (0.0–28.1)	23/0/2	18.0 (6.1.28.5)
17α-OHD	1	1953	21.6	0/0/1	NA
17β-HSD	1	1988	15.0	1/0/0	15.4
StAR mutation	3	1980 (1972–1996)	0.0. (0.0–4.1)	3/0/0	7.0 (0.9–7.8)
WT1 mutation	1	1990	14.0	1/0/0	NA
Unknown	14	1959 (1911–2015)	21.4 (0.0–67.2)	1/1/13	1.6
Total	123	1975 (1911–2012)	14.0 (0.0–67.2)	95/7/21	12.2 (0.6–62.4)
Controls					
Females	12,300	1975 (1911–2012)	NA	NA	NA
Males	12,300	1975 (1911–2012)	NA	NA	NA

Abbreviations: 17α-OHD, 17α-hydroxylase deficiency; 17β-HSD, 17β-hydroxysteroid dehydrogenase deficiency; NA, not applicable; *StAR*, steroidogenic acute regulatory protein gene; *WT1*, Wilms tumor 1 gene.

Statistical analyses

Morbidity, medical prescriptions, mortality, education, retirement, cohabitation, and motherhood were analyzed by using stratified Cox regression. Each XY female and her controls constituted one stratum.

For morbidity, mortality, and medical prescriptions, follow-up started at birth and ended at (1) first date of any hospital admission regardless of diagnosis (overall morbidity); (2) first date of admission with a certain diagnosis (cause-specific morbidity); (3) death (overall mortality); (4) first date of any prescription (overall prescriptions); (5) first date of a specific prescription (cause-specific prescriptions); or (6) first date of emigration, death, or last date of registration, whichever came first.

For education, retirement, cohabitation, and motherhood, follow-up started at the 18th birthday (education, retirement, and cohabitation), the 15th birthday (motherhood), or the start of registration of the event. Follow-up ended at the first occurrence of the event, such as date of first cohabitation, first date of emigration, death, or last date of registration, whichever came first.

Income was analyzed by using conditional logistic regression, with each XY female and her controls constituting one stratum. Retired persons were excluded from the first year of retirement. The median annual income for controls was computed in 5-year intervals, and for each calendar year, a dichotomous variable indicated whether the income for an XY female was higher or lower than the median income in her respective controls in the 5-year interval. The standard error reported is a robust standard error estimate. All comparisons were to female controls unless clearly stated otherwise.

Age at specific events was compared by using the Kruskal-Wallis test. All analyses were performed for the combined cohort of XY females; some were performed with stratification by AIS and GD or by Prader stage (Prader stage 0 and Prader stage ≥ 1). Subgroups of XY females were compared by using the χ^2 test. Ninety-five percent confidence intervals (CIs) were calculated. P values < 0.05 were considered to indicate statistically significant differences. All analyses were performed by using Stata software, version 14.1 (Stata Corp., College Station, TX).

Ethics

The study was approved by the Danish Data Protection Agency (journal number: 2012-41-0047) and the Danish Health Authorities (journal number: 3-3013-472/1/). All data were accessed via a remote desktop access to Statistics. The civil personal registration number of both cases and controls was anonymized by Statistics Denmark.

Results

Overall morbidity

Overall morbidity was increased in XY females as compared with female controls [hazard ratio (HR), 1.72; 95% CI, 1.43 to 2.08] and male controls (HR, 1.82; 95% CI, 1.51 to 2.19) (Fig. 1A). After stratification by the DSD diagnosis, the overall morbidity was increased for both AIS (HR, 1.62; 95% CI, 1.29 to 2.05) and GD (HR, 1.97; 95% CI, 1.27 to 3.05) when compared with female controls (Table 2).

All the following comparisons are made to female controls. Median age at first registered hospital admission was 6.5 years (range, 0.0 to 67.1 years) in XY females and 15.3 years (range, 0.0 to 93.4 years) in controls ($P = 0.0017$). The median age was 6.7 years for AIS (range, 0.0 to 62.4 years) and 4.0 years for GD (range, 0.0 to 25.1 years).

The overall morbidity analysis was repeated with the exclusion of the following diagnostic groups: endocrine, gastrointestinal, and urogenital conditions; congenital malformations; and conditions related to pregnancy and birth. With this approach, no difference in morbidity was observed between XY females and controls (HR, 1.13; 95% CI, 0.93 to 1.37) (Fig. 1B), which applied to both AIS (HR, 1.12; 95% CI, 0.87 to 1.43) and GD (HR, 1.19; 95% CI, 0.74 to 1.90) (Table 2).

Cause-specific morbidity

XY females had increased morbidity according to the following diagnostic groups: congenital malformations; endocrine and gastrointestinal conditions; and external

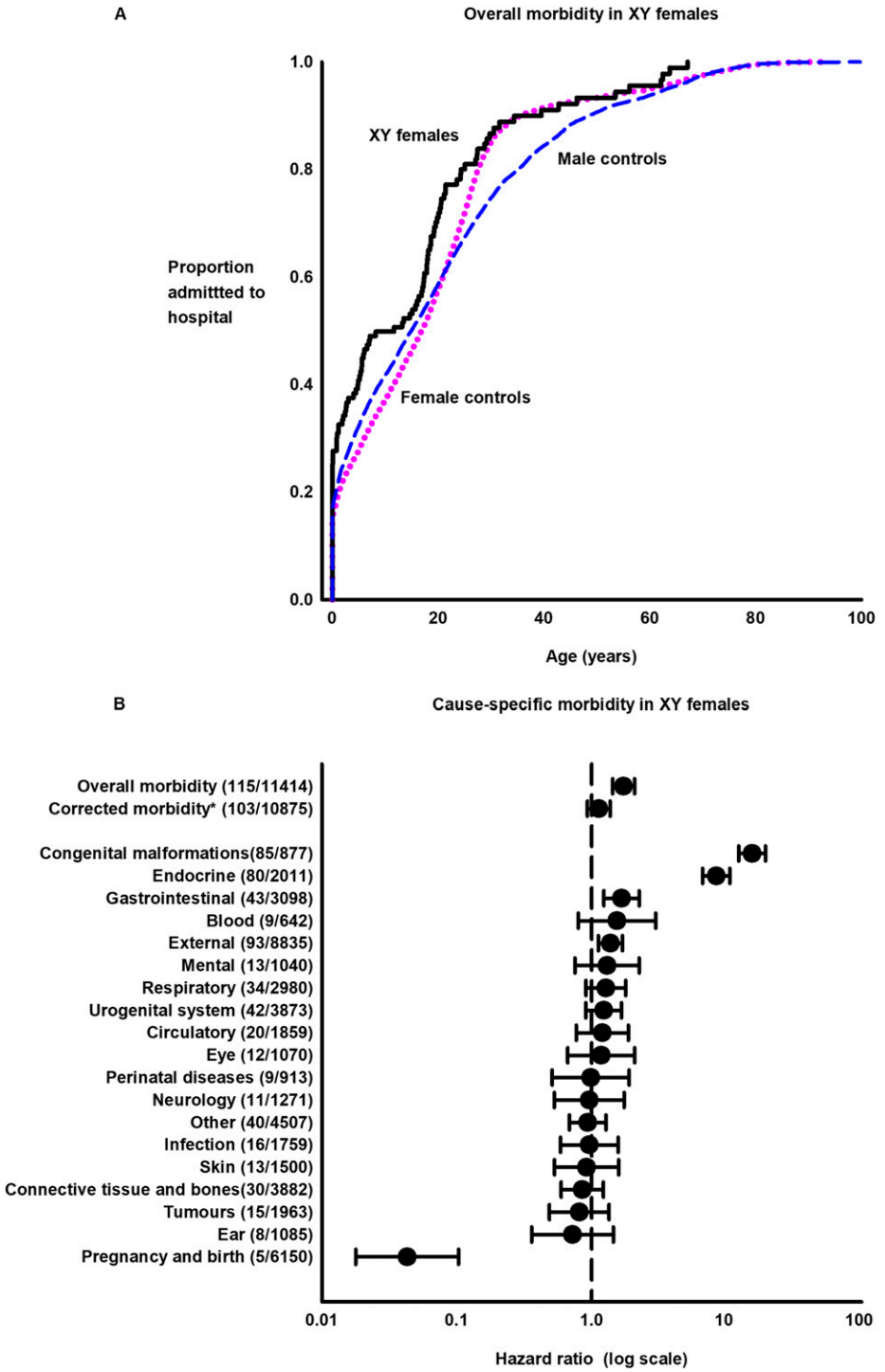

Figure 1. Overall and cause-specific morbidity in XY females. (A) Overall morbidity in XY females expressed as the proportion of XY females (solid line) and female (dotted line) and male (dashed line) controls being admitted to hospital for the first time for any diagnosis. (B) Overall morbidity, corrected morbidity, and cause-specific morbidity in XY females compared with female controls. Error bars are 95% CIs. *First hospital admission for any diagnosis when diagnoses from the following diagnostic groups have been excluded: congenital malformations; endocrine, gastrointestinal, and urogenital conditions; and conditions related to pregnancy and birth.

conditions, including fractures. In contrast, morbidity related to pregnancy and birth was reduced. No difference was observed for the remaining diagnostic groups (Fig. 1B). Morbidity according to specific diagnostic groups or specific diagnoses is listed in Table 3.

Neoplasms

Overall, cancer was not increased in XY females, whereas the risk for gonadal cancer (coded as ovarian cancer in the ICD system) was. Gonadal cancer was observed only in those with GD (n = 2). Three XY females (GD: n = 1; unclassified

Table 2. HRs for Overall and Corrected Morbidity, Overall Medication, Overall Mortality, Education, Retirement, Cohabitation, and Motherhood in XY Females Compared With Female Controls

	Absolute No. of XY Females and Controls				HR (95% CI)		
Variable	AIS	GD	All XY Females	Controls	XY Females	AIS	GD
Overall morbidity	74	21	115	11,414	1.72 (1.43–2.08)	1.62 (1.29–2.05)	1.97 (1.27–3.05)
Corrected morbidity[a]	69	18	103	10,875	1.13 (0.93–1.37)	1.12 (0.87–1.43)	1.19 (0.74–1.90)
Mortality	1	1	6	687	0.79 (0.35–1.77)	NA	NA
Medication	71	22	108	11,208	1.09 (0.90–1.32)	1.18 (0.93–1.50)	1.09 (0.71–1.66)
Socioeconomics							
Education	16	5	24	2826	0.92 (0.61–1.37)	0.90 (0.55–1.47)	0.98 (0.41–2.37)
Retirement	6	0	8	1131	0.76 (0.37–1.55)	1.07 (0.41–2.80)	NA
Cohabitation	31	13	48	6635	0.44 (0.33–0.58)	0.41 (0.29–0.59)	0.51 (0.29–0.88)
Motherhood	3	5	10	5780	0.10 (0.05–0.18)	0.04 (0.01–0.13)	0.29 (0.12–0.70)

Abbreviation: NA, not applicable.

[a]Morbidity was corrected by excluding diagnoses from the following diagnostic groups: congenital malformations; endocrine, gastrointestinal, and urogenital conditions; and conditions related to pregnancy and birth. All diagnostic groups are in accordance with the 10th edition of the International Classification of Diseases.

XY female: n = 2) had a benign gonadal neoplasm (coded as benign ovarian neoplasia). Combined, gonadal neoplasia was observed in 12% (3 of 25) of females with GD. No XY females had a diagnosis of breast cancer.

Endocrine disorders

No difference was observed for type 1 and type 2 diabetes in XY females and controls, nor for thyroid disorders. Pituitary disorders (hypopituitarism and hyperprolactinemia) were increased in XY females.

Mental disorders

Adjustment disorders and encopresis were increased in XY females, whereas no difference of depression and other mood disorders was observed.

Circulatory system

Deep venous thrombosis was increased in XY females, and pulmonary embolism was increased with borderline significance. Median age for these diagnoses was 39.9 years (range, 22.2 to 57.2 years). Cerebrovascular diseases, hypertension, heart diseases, and arteriosclerosis were similar in XY females and controls.

Gastrointestinal disorders

Inguinal hernia, predominantly seen in females with AIS, was increased in XY females.

Urogenital system disorders

Primary amenorrhea and hypertrophy of the breast were increased in XY females.

Connective tissue and bone disorders

There was no difference of osteoporosis between XY females and controls.

Congenital malformations

Malformations of the circulatory system, the musculoskeletal system, and the genitalia and gonads were increased among XY females (see Supplemental Material for further details).

External diseases

Fractures were increased in XY females. After stratification on diagnosis, fractures were increased in females with AIS (HR, 2.15; 95% CI, 1.53 to 3.02) but not in those with GD (HR, 1.30; 95% CI, 0.61 to 2.74).

Mortality

Overall mortality was similar in XY females and controls (HR, 0.79; 95% CI, 0.35 to 1.77) (Table 2). Median age at death was 71.6 years (range, 0.0 to 91.5 years) in XY females and 76.1 years (range, 1.3 to 102.3 years) in controls.

Six XY females died (GD: n = 1; AIS: n = 1; unclassified XY females: n = 4). The causes of death were as follows; GD: malignant neoplasm of the stomach (ICD-10 code: C16.9); AIS: stroke (ICD-10 code: I64.9); unclassified XY females: (1) acute pancreatitis (ICD-8 code: 5770) and chronic pyelonephritis (ICD-8 code: 5900); (2) malignant neoplasm of the kidney (ICD-8 code: 189.0) and cardiac arrest (ICD-8 code: 472.2); (3) coarctation of the aorta (ICD-8 code: 7471); and (4) pneumonia (ICD-10 code: J18.9) and atherosclerotic heart disease (ICD-10 code: I25.1).

Medical prescriptions

Overall, medical prescriptions were not increased among XY females compared to controls (HR, 1.09; 95% CI, 0.90 to 1.32), a finding that applied to both AIS (HR, 1.18; 95% CI, 0.93 to 1.50) and GD (HR, 1.09; 95% CI, 0.71 to 1.66) (Table 2). Sex hormone prescriptions and urogenital system precriptions were increased, whereas cardiovascular and

Table 3. Cause-Specific Morbidity in XY Females

Diagnosis	ICD-10 Code	ICD-8 Code	AIS (n)	GD (n)	All XY Females (n)	Controls (n)	HR (95% CI)
Infections	A00–B99	000–136	9	3	16	1759	0.96 (0.59–1.57)
All neoplasms	C00–D48	140–239	6	6	15	1963	0.81 (0.49–1.35)
Malignant neoplasm, overall	C00–C97	140–209	0	2	4	590	0.74 (0.28–1.98)
Malignant neoplasm of breast	C50	174	0	0	0	178	NA
Malignant neoplasm of ovary[a]	C56	183	0	2	2	34	7.53 (1.75–32.37)
Malignant neoplasm of female genital organs	C51–C55, C57	180–182, 184	0	0	0	65	NA
Malignant neoplasm of testis[a]	C62	186	0	0	0	0	NA
Malignant neoplasm of urinary tract	C64–C68	188–189	0	0	1	20	6.23 (0.81–47.73)
Benign neoplasms, overall	D10–D36	210–228	6	2	10	1416	0.74 (0.40–1.38)
Benign neoplasm of ovary[a]	D27	220	0	1	3	239	1.38 (0.44–4.31)
Uncertain neoplasms, overall	D37–D48	230–239	0	1	2	249	0.87 (0.22–3.51)
Uncertain neoplasm of ovary[a]	D39.1	235	0	0	0	6	NA
Blood	D50–D89	280–289	3	3	9	642	1.54 (0.79–2.98)
Anemia	D50–D64	280–285	3	1	5	306	1.78 (0.73–4.35)
Endocrinology	E00–E90	240–279	63	5	80	2011	8.38 (6.64–10.57)
Diabetes mellitus type 1	E10	249	3	0	3	128	2.69 (0.85–8.51)
Diabetes mellitus type 2	E11	250	1	0	1	240	0.86 (0.21–3.46)
Disorders of thyroid gland	E00–E07	240–246	0	0	2	520	0.40 (0.10–1.62)
Disorders of parathyroid glands	E20–E21	252	0	1	1	39	2.79 (0.38–20.50)
Disorders of pituitary gland	E22–E23	253	1	1	4	41	11.48 (4.05–32.53)
Hyperprolactinemia	E22.1	NA	1	0	1	11	12.25 (1.51–99.65)
Pituitary insufficiency	E23	25318, 25319	0	1	3	20	17.05 (4.93–58.97)
Cushing	E24	25800–25809	1	0	1	12	10.55 (1.32–84.39)
Adrenogenital disorders	E25	25501, 27360–27369	3	0	7	1	582.18 (70.70–4794.00)
Gonadal dysfunction	E28–E29	25609–25719	2	2	4	82	5.59 (2.03–15.38)
Disorders of puberty	E30	25891–25892	1	0	0	35	3.21 (0.44–23.58)
AIS	E34.5	25790	58	2	66	0	NA
Psychiatry	F00–F99	290–315	9	3	13	1040	1.30 (0.75–2.25)
Depression and unspecified mood disorders	F32–F39	30049	1	0	1	178	0.54 (0.08–3.88)
Adjustment disorders	F43.2	30806	3	1	5	25	23.34 (8.71–62.56)
Nonorganic encopresis	F98.1	30679	2	0	2	12	16.20 (3.62–73.37)
Neurology	G00–G99	320–358	6	2	11	1271	0.96 (0.53–1.74)
Ophthalmology	H00–H59	360–379	6	1	12	1070	1.18 (0.66–2.08)
Otology	H60–H95	380–389	4	3	8	1085	0.72 (0.36–1.45)
Circulatory system diseases	I00–I99	390–458	13	4	20	1859	1.20 (0.77–1.87)
Heart diseases	I00–I02, I30–I33, I38–I52	390–393, 415–429, 441–448	3	2	6	509	1.22 (0.55–2.75)
Ischemic heart disease and atherosclerosis	I20–I25, I70	410–414, 440	1	0	1	348	0.31 (0.04–2.22)
Heart valve disorders	I05–I09, I34–I37	394–396	2	0	2	77	2.32 (0.56–9.54)
Hypertension	I10–I15	400–404	2	1	4	535	0.92 (0.34–2.47)
Cerebrovascular diseases	I60–I69.8	430–438	3	0	4	267	1.44 (0.53–3.87)
Thrombophlebitis and thrombosis of the veins	I80–I82.9	451–453	3	1	5	133	4.11 (1.67–10.09)
Pulmonary embolism	I26	450	1	0	2	46	3.84 (0.92–15.98)
Respiratory system	J00–J99	460–519	18	9	34	2980	1.27 (0.91–1.79)
Acute infections, including pneumonia	J00–J22	460–486	9	6	21	1610	1.45 (0.94–2.23)
Chronic lower respiratory diseases	J40–J47	490–493	3	0	5	699	0.76 (0.31–1.83)
Diseases of upper respiratory tract, excluding acute infections	J30–J39	500–508	10	4	15	1296	1.20 (0.72–2.01
Other respiratory diseases	J60–J99	510–519	1	1	3	201	1.69 (0.54–5.32)
Gastrointestinal	K00–K93	520–577	31	7	43	3098	1.66 (1.23–2.25)

(*Continued*)

Table 3. Continued

Diagnosis	ICD-10 Code	ICD-8 Code	AIS (n)	GD (n)	All XY Females (n)	Controls (n)	HR (95% CI)
Inguinal hernia	K40	550	21	2	23	139	20.14 (12.83–31.61)
Diseases of gall system	K80–K87	574–576	2	1	5	512	1.14 (0.47–2.75)
Skin	L00–L99	680–709	8	2	13	1500	0–92 (0.53–1.58)
Connective tissue and bones	M00–M99	710–738	17	6	30	3882	0.85 (0.59–1.22)
Osteoporosis	M80–M82	72309	2	0	3	173	1.74 (0.55–5.49)
Urogenital	N00–N99	580–629	23	14	42	3873	1.23 (0.90–1.67)
Kidney and urinary system diseases	N00–N39	580–599	5	2	9	1233	0.74 (0.38–1.43)
Breast disorders	N60–N64	610–611	8	2	10	581	2.06 (1.10–3.85)
Hypertrophy of the breast	N62	61110–61119	6	0	6	144	4.54 (2.00–10.62)
Diseases of female internal and external genitalia	N70–N90	612–625	4	3	8	1743	0.48 (0.24–0.96)
Menstruation disorders	N91–N96	626–627	8	11	21	1371	1.83 (1.18–2.82)
Infertility	N97–N98	628–628	1	7	8	559	1.59 (0.79–3.21)
Pregnancy and birth	O00–O99	630–678	0	4	5	6150	0.04 (0.02–0.10)
Perinatal disease	P00–P96	760–779	4	2	9	913	0.98 (0.51–90)
Congenital malformations	Q00–Q99	740–759	54	17	85	877	15.45 (12.28–19.44)
Nervous system	Q00–Q07	740–743	0	0	1	45	2.42 (0.33–17.61)
Circulatory system	Q20–Q28	746–747	3	0	4	124	3.41 (1.26–9.26)
Respiratory system	Q30–Q34	748	0	0	0	23	NA
Digestive system	Q35–Q45	749–751	1	0	1	55	1.90 (0.26–13.77)
Genitalia and gonads	Q50–Q56	752	45	9	64	73	142.95 (96.83–211.02)
Urinary system	Q60–Q64	753	0	0	0	65	NA
Musculoskeletal system	Q65–Q79	754–756	4	0	7	271	2.69 (1.27–5.70)
Other diagnoses	R00–R99	780–796	21	8	40	4507	0.94 (0.68–1.28)
External	S00–T98; V00–Y09	800–999; E8000–E9999	65	16	93	8835	1.38 (1–12–1.69)
All fractures	S02, S12, S22, S32, S42, S52, S62, S72, S82, S92, T8, T10, T12	800–829	34	7	44	3024	1.66 (1.23–2.24)
Potential osteoporotic fractures	S12.0–S12.7, S32.0, S52, S72.0–S72.2	805, 813, 820	11	2	15	1082	1.48 (0.89–2.48)

HRs shown for specific diagnoses. All comparisons are between XY females and female controls. Abbreviation: NA, not applicable.

[a] Gonadal neoplasms are coded as ovary neoplasm or testicular neoplasms in the ICD system.

dermatologic prescriptions were reduced (Supplemental Fig. 1). There was no difference of antidepressive prescriptions (HR, 0.77; 95% CI, 0.49 to 1.19) between XY females and controls, neither with stratification by Prader stage ($HR_{Prader=0}$, 0.71; 95% CI, 0.38 to 1.23 and $HR_{Prader\geq1}$, 1.26; 95% CI, 0.62 to 2.53). In a comparison of nonvirilized XY females (Prader score of 0) with virilized XY females (Prader score $\geq$ 1), significantly more of those who were virilized had an antidepressive agent prescribed (χ^2 = 0.05). HRs of more specific prescriptions are shown in Table 4.

Socioeconomics

Cohabitation

Cohabitation was reduced in XY females (HR, 0.44; 95% CI, 0.33 to 0.58) (Fig. 2A), and it was reduced in both those with AIS (HR, 0.41; 95% CI, 0.29 to 0.59) and those with GD (HR, 0.51; 95% CI, 0.29 to 0.88) (Table 2) as well as after stratification by Prader stage [$HR_{Prader=0}$, 0.42 (95% CI, 0.30 to 0.60); $HR_{Prader\geq1}$, 0.47 (95% CI, 0.29 to 0.76)]. The median age at first cohabitation was 24.9 years (range, 18.1 to 46.5 years) in XY females and 22.1 years (range, 18.1 to 69.7 years) in controls.

Motherhood

Motherhood was reduced in XY females (HR, 0.10; 95% CI, 0.05 to 0.18) (Fig. 2B), and this applied to both AIS and GD (Table 2).

Education

XY females and controls had the same level of education (HR, 0.92; 95% CI, 0.61 to 1.37) (Fig. 2C), which applied to both AIS (HR, 0.90; 95% CI, 0.55 to 1.47) and

Table 4. Prescribed Medication in XY Females Compared With Female Controls

Prescription	ATC Code	AIS (n)	GD (n)	All XY Females (n)	Controls (n)	HR (95% CI)
Antidiabetics	A01	3	0	4	435	1.01 (0.38–2.72)
Oral contraceptives	G03A	6	3	9	7364	0.06 (0.03–0.11)
Androgens	G03B	2	0	3	1	175.12 (15.81–1939.27)
Estrogens	G03C	58	16	84	1160	16.64 (13.15–21.07)
Progesterone and estrogen, combined	G03F	16	18	41	466	16.27 (11.64–2.73)
Bisphosphonates	M05BA–M05BB	0	1	2	205	1.16 (0.29–4.67)
Antidepressives	N06A	15	3	20	2712	0.77 (0.49–1.19)

Abbreviation: ATC, Anatomical Therapeutic Chemical Classification System.

GD (HR, 0.98; 95% CI, 0.41 to 2.37) (Table 2). Median age of achieving an education was 25.4 years (range, 22.9 to 35.9 years) in XY females and 25.6 years (range, 21.0 to 44.7 years) in controls.

Income

XY females' income differed from the median income in controls. As such, XY females had a lower income from 20 to 29 years of age, a similar income from 30 to 49 years of age, and a higher income from 50 to 59 years of age (Fig. 2D).

Retirement

Retirement was similar in XY females and controls (HR, 0.76; 95% CI, 0.37 to 1.55). After stratification by diagnosis, there was no difference between females with AIS and controls (HR, 1.07; 95% CI, 0.41 to 2.80). No retirements were observed for GD (Table 2). The median age at retirement was 46.0 years in XY females (range, 21.0 to 68.0 years) and 53.0 years in controls (range, 19.0 to 74.0 years).

Discussion

This study comparing XY females with the general population shows that XY females have an increased overall morbidity, but not mortality, related to their specific condition. In terms of socioeconomic factors, XY females fared similarly to controls concerning education, income, and retirement, whereas both cohabitation and motherhood were reduced in XY females. Overall, XY females with AIS and GD had a similar trajectory of health and socioeconomic factors.

Overall morbidity was increased in XY females, when observing any first hospital admission. As expected, XY females had an increased morbidity related to the diagnostic groups of congenital malformations and endocrine and gastrointestinal conditions because these encompass the diagnoses of the DSD condition itself [e.g., AIS and CAH (endocrine conditions)], diagnoses associated to the cause of being diagnosed with DSD [inguinal hernia (gastointestinal conditions)], or diagnoses of malformations related to genitalia and gonads. Primary amenorrhea, another likely cause of DSD diagnosis, is included in the diagnostic group of urogenital conditions, and XY females had an increased incidence of primary amenorrhea; however, the overall urogenital morbidity was not increased. As expected, morbidity related to pregnancy and birth was reduced. When we estimated morbidity after excluding the above-mentioned diagnostic groups, no difference between XY females and controls was observed. This observation was substantiated by the similarity in overall medical prescriptions comparing XY females and controls.

Gonadal malignancy was increased in XY females with GD (Table 3). After pooling of XY females with GD, who were registered as having benign gonadal tumors or gonadal cancer, the total prevalence of gonadal tumors was 12%. As such, the prevalence of gonadal tumors in GD in this study is within the range of previous estimates (10% to 60%). Concerning CAIS, consensus today is to postpone gonadectomy until after puberty if the *AR* mutation is known (22), and sometimes even beyond that. Thus, evidence of the safety of postponing gonadectomy is requested. In the current study, no XY female with AIS was diagnosed with a gonadal tumor. However, 92% of females with AIS included in the study had undergone gonadectomy at a median age of 8.3 years (Table 1) (1). We have no data on the gonadal histology in patients with AIS or GD; thus, this study cannot provide valid data on the risk for gonadal tumors in XY females.

Overall, XY females had no increased occurrence of circulatory system diseases, particularly not of ischemic heart disease, arteriosclerosis, hypertension, and cerebrovascular disease. Furthermore, a reduced occurrence of prescriptions related to cardiovascular disease was observed. This observation substantiates that the cardiovascular status in the present cohort of XY females at the end of follow-up was unaffected by the DSD even though severe estrogen deficiency due to nonadherence to treatment or due to periods with loss to medical follow-up could have led to an increased occurrence of cardiovascular events. Type 2 diabetes was also not

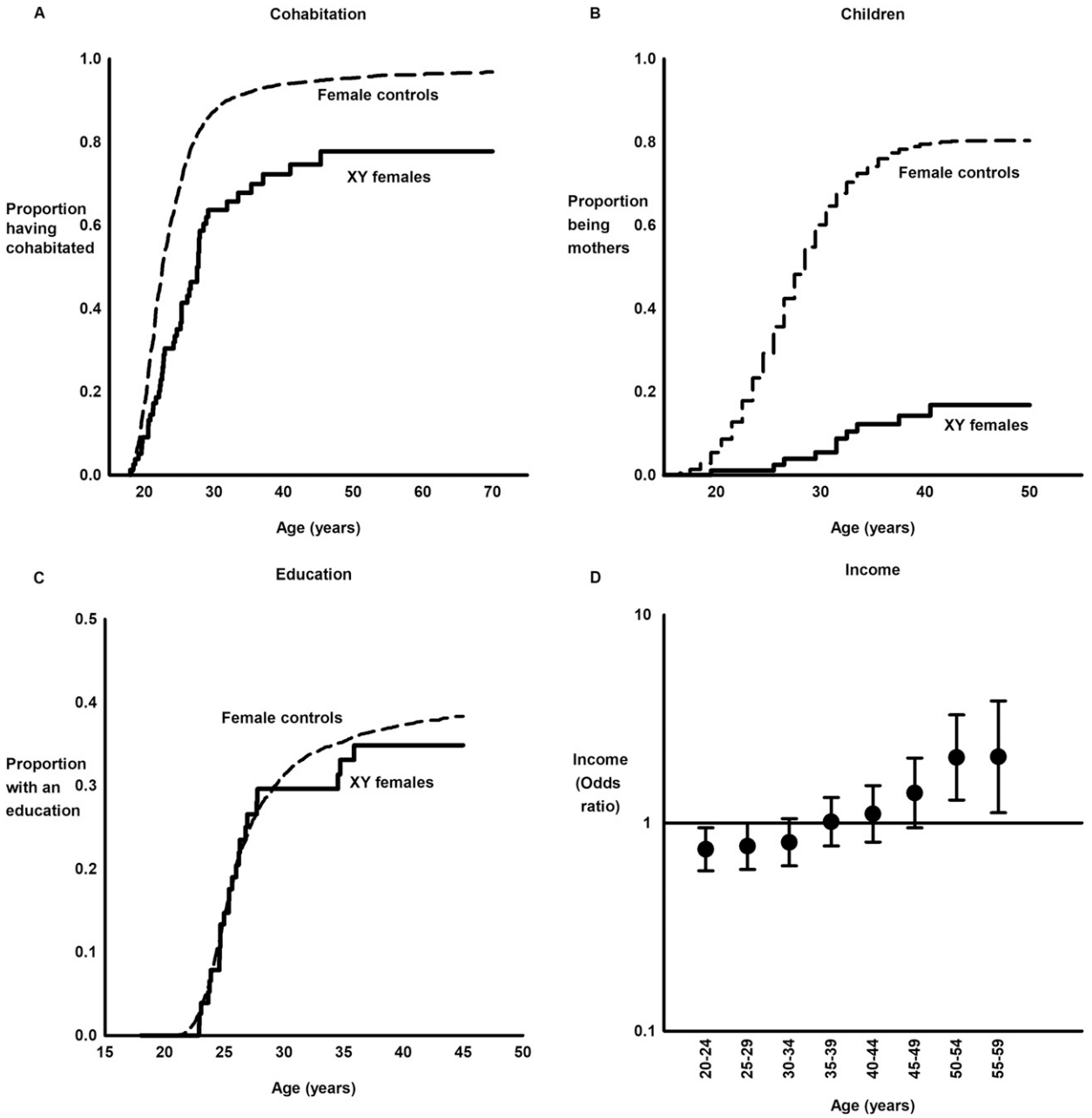

Figure 2. Socioeconomics in XY females compared with female controls. (A) Proportion living with a partner for the first time. (B) Proportion becoming mothers for the first time (adopted children are included in the analysis). (C) Proportion achieving an education (defined as a bachelor's degree or higher). (D) Odds ratio of XY females having an income similar to, above, or below the median income in controls. All comparisons are made to female controls. Error bars are 95% CIs.

increased in XY females. However, XY females were comparatively young at the end of follow-up (median age, 32.5 years; range, 0.0 to 91.5 years); thus, the deleterious effects of estrogen deficiency may not yet have appeared. In contrast, we observed an increased occurrence of DVT and pulmonary embolism with borderline significance. This could be due to hormone treatment. Only one of seven women registered with venous thromboembolism was treated with oral contraceptives which, at least in perimenopausal or postmenopausal women, seem to carry a higher risk for venous thromboembolism than does estradiol treatment alone (23). Concerning sex hormone treatment, it was surprising that 16 XY females with AIS received treatment with a combination of estrogen and progesterone.

Fractures were increased among XY females. This is considered to be associated with reduced bone health, although occurrence of osteoporosis or prescriptions of bisphosphonates did not differ from controls. Previously, bone mineral density was reported as being lower in XY females with GD than in XY females with CAIS (14). We, on the other hand, observed an increased occurrence of

fractures in AIS only. However, this may be due to lack of statistical power in the GD subgroup.

No difference was observed for the occurrence of type 1 diabetes or thyroid disorders, both of which are common in, for example, Turner syndrome (18). However, the occurrence of hypopituitarism was increased. We speculate whether this is due to misdiagnosis of hypergonadotropic hypogonadism, even though it has been suggested that long-standing hypogonadism may lead to compensatory development of a gonadotrophic pituitary adenoma (24). In case of hypopituitarism, hormones are prescribed by the hospital pharmacy; thus, the MSR does not hold this information and, therefore, we were unable to validate the diagnosis of hypopituitarism by hormone prescriptions registered in the MSR.

Outcomes of studies concerning quality of life in DSD have been equivocal, ranging from reduced quality of life to similar or even better quality of life than among controls (25–27). Generally, virilized XY females have inferior outcomes compared with nonvirilized XY females. In the current study, the occurrence of diagnosed depressions and the occurrence of prescribed antidepressives did not differ between XY females and controls. However, significantly more virilized XY females had prescriptions for antidepressives than did nonvirilized XY females, supporting the reports of reduced psychological well-being due to virilization.

XY females were less likely to cohabitate than controls, and cohabitation occurred later in life, regardless of diagnosis (AIS or GD) and Prader stage. This may be due to a negative effect of the DSD condition on self-esteem and person's expectations. We find this substantiated by the increased occurrence of adjustment disorders among XY females. Other studies have likewise reported XY females being less likely to engage in relationships (28, 29), although Hines *et al.* (30) found the prevalence of relationships similar in CAIS and controls. We speculate whether receiving a DSD diagnosis influences the likelihood of cohabitating, thus leading to impairment of cohabitation after but not before the DSD diagnosis. In the current study, however, 75% of patients were diagnosed by the age of 18 years, *i.e.*, before the time in life when cohabitation normally takes place. XY females with a uterus can achieve motherhood through oocyte donation (31). Nevertheless, motherhood was rare among XY females, although our data included XY females who became mothers to adopted children.

Education was similar in XY females and controls. Concerning income, XY females had a higher income than the median income in controls from an age around the mid-40s and onward, suggesting that XY females generally perform well on the labor market. This is in line with an Italian study reporting more XY females with a university degree than in the general Italian population (28). A German study reported approximately 65% (n = 8/12) of nonvirilized XY females with a high to very high educational level (26). We have no obvious explanations for the reduced income in XY females in the younger age groups in the current study, but previously we observed a similar pattern in Turner syndrome (21). We speculate whether XY females are more unsure of themselves in their younger years and whether this leads to increased parental support, including financial support. Thus, the need to have a job and earn money may be lower in XY females than in the general population.

The strength of the current study is the nationwide approach, which minimizes selection bias; such bias is often present in studies requiring active participation. Furthermore, the close matching with controls enables a strong comparison with the general population. The complete follow-up allows accounting for changes in specific outcomes over time. Limitations are the risk for misclassification, applicable to all epidemiologic studies, and the lack of a specific diagnosis in 15 XY females.

In conclusion, XY females have an overall morbidity similar to that of the female background population in terms of diagnoses unrelated to the DSD condition *per se*. In contrast, the DSD condition seems to reduce the likelihood of both cohabitating and having children, even when adoptions are taken into account. The proportion of XY females who achieved an education was similar to female controls, and on the basis of the income in the older years, XY females seem to perform well in the labor market.

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