Genetics in Medicine (2022) 24, 475–487

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Genetics in Medicine

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ARTICLE

The comorbidity landscape of 47,XXX syndrome: A nationwide epidemiologic study

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ARTICLE INFO

Article history:
Received 25 May 2021
Revised 21 September 2021
Accepted 20 October 2021
Available online 30 November 2021

Keywords:
47,XXX
46,XX/47,XXX
Triple X syndrome
Trisomy X

ABSTRACT

Purpose: This study aimed to describe the comorbidity pattern in 47,XXX syndrome.
Methods: This was a registry-based study of hospital diagnoses and prescribed medication in a nationwide cohort of females with 47,XXX (n = 103) and 46,XX/47,XXX (n = 57) in which they were compared with 16,000 age-matched general population female controls.
Results: The overall occurrence of hospital diagnoses was significantly increased in females with 47,XXX when compared with controls (incidence rate ratio = 2.1, CI = 1.7-2.5), and when divided into 19 organ-specific groups, there was a significantly increased risk in the following 14 groups: infection, blood, endocrine and metabolism, mental, nervous system, eye, ear, respiratory, oral cavity and gastrointestinal, musculoskeletal, perinatal, congenital malformations, external factors, and "other." The risk of being prescribed any medication was not significantly increased in females with 47,XXX when compared with controls (hazard ratio = 1.2, CI = 0.9-1.4). However, when stratified according to medication groups, a significantly increased risk was detected in 4 of 13 groups. The overall occurrence of hospital diagnoses was also significantly increased when females with 46,XX/47,XXX were compared with controls (incidence risk ratio = 1.3, CI = 1.01-1.8), but generally, in comparison with controls, females with 46,XX/47,XXX were less severely affected than females with 47,XXX.
Conclusion: The 47,XXX syndrome is associated with an increased occurrence of a wide variety of diseases. Increased awareness of this may contribute to improve counseling and clinical assessment of these patients.

Introduction

The 47,XXX syndrome is caused by the presence of an extra X chromosome in females. It was first reported in 1959 in a young woman with tall stature, secondary amenorrhea, and infantile genitalia.[1] Since then, the associated phenotype has been very variably described, ranging from asymptomatic to subtle and nonspecific physical features to significant neurodevelopmental challenges,[2] including learning disabilities, developmental delay, and behavioral disorders.[3-5] In addition, a variety of congenital malformations[6] and medical conditions has been reported.[7,8]

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doi: https://doi.org/10.1016/j.gim.2021.10.012

The 47,XXX syndrome is not a very rare syndrome. It has been estimated to affect 84 per 100,000 newborn girls.[9] Nondiagnosis is, however, a pervasive challenge, and less than 15% of affected girls and women are clinically ascertained. Furthermore, diagnosis is often considerably delayed, and some are not diagnosed until late in life.[9] The low diagnostic rate is likely a result of the variable phenotype, in which features may not meet the threshold for a genetic analysis, or clinicians may under-recognize symptoms as features of the 47,XXX syndrome, thus not obtaining a chromosome analysis.

When facing a diagnosis of 47,XXX syndrome, several questions and concerns may arise, including concerns regarding long-term health outcomes. Knowledge within this field is, however, limited and often based on case reports or small selected cohorts, except for 2 population-based studies that have reported a significantly increased mortality in patients with 47,XXX syndrome when compared with the background population.[7,10] This makes comprehensive counseling of patients and parents regarding what to expect for the future difficult and, especially in the prenatal setting, poses a great challenge.

To add to the knowledge regarding possible associations between the 47,XXX syndrome and long-term health outcomes, we present data from a nationwide epidemiological study of the Danish 47,XXX and 46,XX/47,XXX cohort. We have undertaken a systematic and comprehensive analysis of longitudinally collected hospital diagnoses and medical prescriptions to describe the pattern of general and cause-specific comorbidity within this cohort in comparison with controls.

Materials and Methods

Setting

In Denmark, all residents are offered universal, tax-supported health care, herein genetic analyses, from both general practitioners and hospitals by the Danish National Health Service.

Data sources

Denmark has a large network of government-maintained, fully automated population-based health and administrative registries in which high-quality individual-level data of all Danish residents are recorded.

Linkage of data from the different registries is possible via the unique 10-digit identification number assigned to all residents at birth or upon immigration. Statistics Denmark is the central authority of the registries.

The Danish Cytogenetic Central Registry (DCCR) contains data on all individuals who have received a chromosome analysis in Denmark since 1960. Information regarding the phenotype and indication for doing a genetic analysis is not available nor is consistent information on the percentage of mosaic cell lines.

The Danish National Patient Registry has collected inpatient data from all Danish hospitals since 1977, including admission dates and diagnoses (primary and secondary), according to the Eighth (1977-1993) and 10th (1994-) revision of the International Classification of Diseases (ICD-8 and ICD-10). Outpatient data and data from psychiatric hospital departments have been collected since 1995.

The Danish National Database of Reimbursed Prescriptions contains data on all prescriptions for all types of medication since 1995, including date of reimbursement and medication code according to the Anatomical Therapeutic Chemical Classification System (ATC). Medication use during hospitalization and prescriptions administered by hospital pharmacies is not included.

End of follow-up was December 31, 2014.

Patients and controls

The DCCR was searched for all individuals registered with the sex chromosome costitution 47,XXX or 46,XX/47,XXX during 1960 to 2014. All chromosome analyses were performed postnatally. For an unknown subset of patients, the chromosome analysis was performed to verify a prenatally obtained karyotype. Statistics Denmark established a comparison cohort by age-matching each case with 100 random female controls from the Danish general population. The following data were retrieved for cases and controls: (1) diagnosis codes and dates of diagnoses, (2) ATC codes and dates of reimbursement of prescriptions, (3) date of death, and (4) date of emigration.

Statistics

Hospital diagnoses were analyzed by negative binomial regression yielding incidence rate ratios (IRRs) as the measure of the association. Each stratum of a female patient with 47,XXX syndrome and her matched controls constituted a cluster. This clustering was allowed for using a random effects model.

The prescribed medication was analyzed by stratified Cox regression yielding hazard ratios (HRs) as the measure of association. A Cox regression analysis was also performed for the first registration of any hospital diagnosis.

For the negative binomial regression analysis, time at risk started at birth and ended at death, at emigration, or at the end of follow-up, whichever came first, for the Cox regression analyses, time at risk started at birth and ended at first registration of the diagnosis/prescription of interest and ended at death, at emigration, or at the end of follow-up, whichever came first.

All analyses were stratified according to karyotype, namely 47,XXX or 46,XX/47,XXX. IRRs and HRs for subanalyses of hospital diagnoses and prescribed medication

were provided in case of a statistically significant difference between either patients with 47,XXX and controls or between patients with 46,XX/47,XXX and controls. If significant, but with the event of interest observed for only 1 case, the results are not provided because the level of incidence may go beyond pure coincidence.

All analyses were performed using StataCorp. 2019. Stata Statistical Software: Release 16 (StataCorp LLC, College Station, TX). $P < .05$ was considered to be statistically significant.

Data were accessed by a secure remote access to Statistics Denmark. To avoid the possibility of personal identification, Statistics Denmark prohibits specification of the exact number of cases with a given registration if <4, and thus, the number of cases are reported here as $n < 4$.

Results

A total of 163 females with a 47,XXX or 46,XX/47,XXX karyotype were registered in the DCCR during 1960 to 2014. Of those, 2 were excluded because of an invalid identification number and 1 because of a registration error, leaving a study cohort of 160 females (47,XXX: $n = 103$; 46,XX/47,XXX: $n = 57$) and 16,000 controls. The period from the start of registration to the end of study was 38 years for hospital diagnoses (47,XXX: 3651 person-years; 46,XX/47,XXX: 1819 person-years) and 19 years for reimbursed prescriptions (47,XXX: 1797 person-years; 46,XX/47,XXX: 793 person-years). Mean age at the end of follow-up was 29.2 years for 47,XXX and 53.8 years for 46,XX/47,XXX.

Hospital diagnoses

Both 47,XXX and 46,XX/47,XXX were associated with a significant increased occurrence of hospital diagnoses compared with controls (47,XXX: IRR = 2.1, CI = 1.7-2.5; 46,XX/47,XXX: IRR = 1.3, CI = 1.01-1.8) (Figure 1A and B), and the time to first registration of any hospital diagnosis was significantly reduced for those with 47,XXX and 46,XX/47,XXX when compared with controls (47,XXX: HR = 1.4, CI = 1.1-1.8; 46,XX/47,XXX: HR = 1.4, CI = 1.04-1.8) (Figure 2).

Dividing diagnoses into organ-specific groups according to ICD-10 chapters, females with 47,XXX had significantly more registrations of diagnoses than controls in 14 of 19 chapters (Figure 1A, Table 1) and females with 46,XX/47,XXX had significantly more registrations than controls in 4 chapters (Figure 1B, Table 1).

Among females with 47,XXX, diagnoses of mental and behavioral disorders were significantly increased overall, and specifically, there was an increased risk of intellectual disability, behavioral, and emotional disorders and of disorders of speech, language, and scholastic skills. Intellectual disability was also significantly increased among females with 46,XX/47,XXXX.

Infertility and recurrent miscarriages were substantially increased in females with 46,XX/47,XXX but not in females with 47,XXX, whereas both groups had an increased occurrence of pregnancies with abortive outcome and hemorrhage in early pregnancy. Among females with 47,XXX, we found an increased occurrence of diagnoses related to absent, scanty, and rare menstruation cycles.

Diagnoses related to congenital malformation and genetic conditions occurred much more frequently in females with 47,XXX and females with 46,XX/47,XXX compared with controls, and among females with 47,XXX, the variety of malformations extended to virtually every organ system. Disorders related to the perinatal period were significantly more common in both groups.

Concerning diagnoses related to endocrine and metabolic disorders, type 2 diabetes and diabetes in pregnancy were significantly increased among females with 47,XXX but not among those with 46,XX/47,XXX. Conversely, females with 46,XX/47,XXX, but not those with 47,XXX, had an increased occurrence of osteoporosis.

Among other diagnoses observed with increased frequency in females with 47,XXX but not in those with 46,XX/47,XXX were thrombophilia, venous thrombosis and pulmonary embolism, episodic and paroxymal disorders, a variety of eye disorders, hearing loss, pneumonia and asthma, dental disorders, constipation, cholelithiasis, and certain infectious diseases (Table 1).

Prescribed medication

The overall risk of having any medication prescribed did not differ significantly from controls for females with 47,XXX (HR = 1.2, CI = 0.9-1.4) nor for females with 46,XX/47,XXX (HR = 1.1, CI = 0.8-1.4) (Figure 3A and B). However, because of the massive comorbidity as interpreted from registrations of hospital diagnoses, we also divided prescribed medication in groups according to the Anatomical Therapeutic Chemical System classification.

Thereby, for both females with 47,XXX and those with 46,XX/47,XXX, we observed a significant increased risk of being prescribed medication related to the alimentary tract and metabolism. Moreover, females with 47,XXX had a significantly increased risk of being prescribed medication related to the nervous and respiratory system in addition to medication related to eye and ear. Dermatologicals and antineoplastic and immunomodulating medication were significantly increased in females with 46,XX/47,XXX (Figure 3A and B, Table 2). Sex hormone replacement therapy was significantly increased in both groups and contraceptives for systemic use were significantly decreased in females with 47,XXX (Table 2).

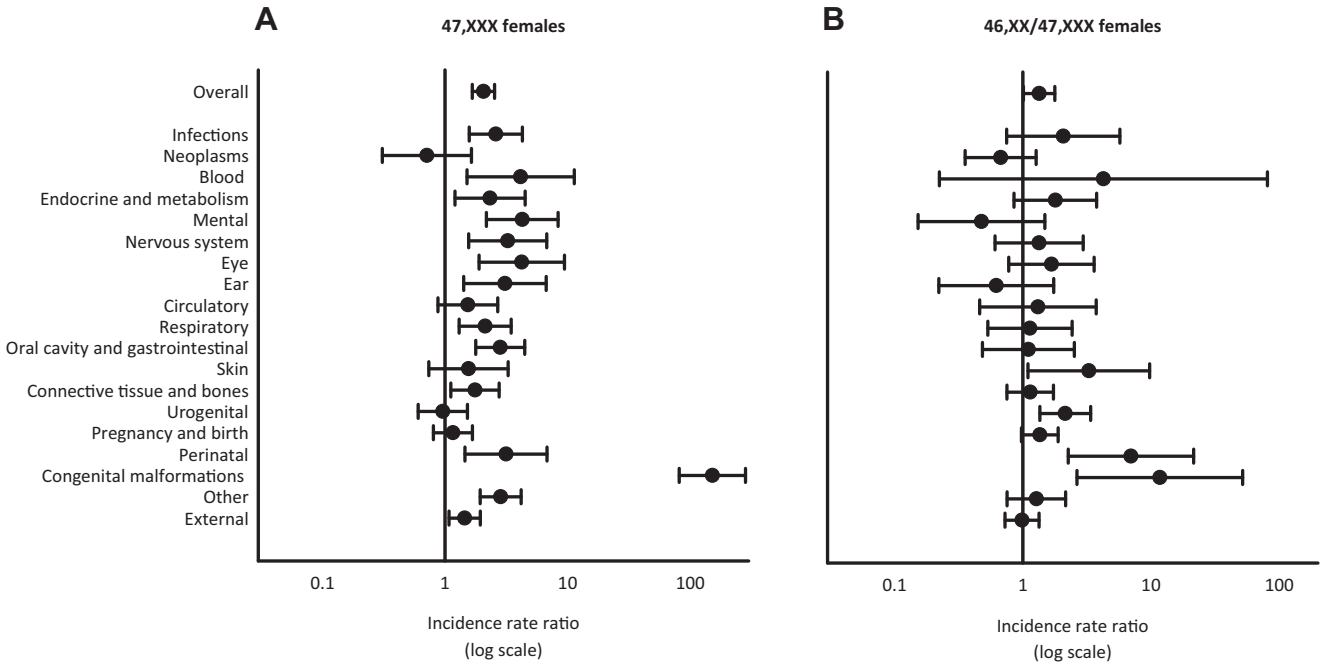

Figure 1 **Hospital diagnoses in females with 47,XXX syndrome**. Diagnoses are divided into chapters according to the 10th Revision of International Classification of Diseases. A. Females with 47,XXX. B. Females with 46,XX/47,XXX.

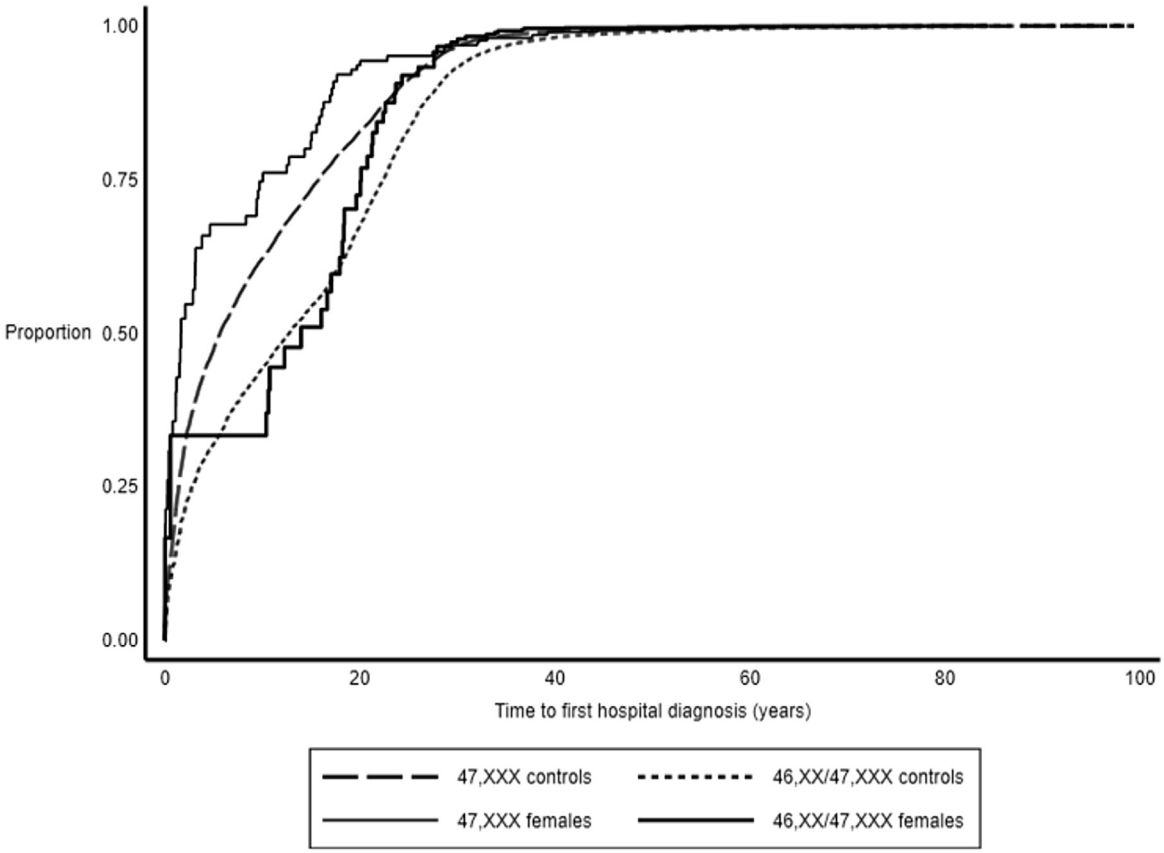

Figure 2 **Time to first hospital diagnosis in females with 47,XXX syndrome**. Proportion of females with 47,XXX and females with 46,XX/47,XXX and their controls being registered with a hospital diagnosis for the first time. Please note that the age-matched control groups for the 47,XXX and the 46,XX/47,XXX groups do not follow the same trajectory. This is because the control group for the 46,XX/47,XXX group is considerably older than the control group for the 47,XXX group.

Table 1 Hospital diagnoses in 47,XXX syndrome

Diagnosis	ICD-10 Code	ICD-8 Code	Number of Females With 47,XXX (%)	Number of Controls (%)	IRR (95% CI)	Number of Females with 46,XX/ 47,XXX (%)	Number of Controls (%)	IRR (95% CI)
Infectious diseases	A-B	000-136	29 (28.2)	1547 (15.0)	2.6 (1.6-4.3)	10 (17.5)	818 (14.4)	2.1 (0.7-5.7)
Neoplasms	C00-D48	140-239	8 (7.8)	1380 (13.4)	0.7 (0.3-1.6)	16 (28.1)	1724 (30.2)	0.7 (0.4-1.3)
Blood and blood-forming organs	D50-D89	280-289	9 (8.7)	350 (3.4)	4.1 (1.5-11.3)	5 (8.8)	363 (6.4)	4.3 (0.2-80.9)
Aplastic and other anemias	D60-D64	284-285	5 (4.9)	131 (1.3)	6.6 (1.9-23.2)	<4 (<7.0)	195 (3.4)	1.1 (0.3-4.0)
Coagulation defects, other	D68	286	4 (3.9)	43 (0.4)	38.8 (7.1-213.7)	0 (0)	32 (0.6)	NA
Thrombophilia	D685	NA	4 (3.9)	23 (0.2)	57.8 (16.9-198.1)	0 (0)	10 (0.2)	NA
Endocrine and metabolism	E	240-279	22 (21.4)	1483 (14.4)	2.3 (1.2-4.5)	17 (29.8)	1367 (24.0)	1.8 (0.9-3.8)
Diabetes type 2	E119	250	5 (4.9)	133 (1.3)	5.7 (1.3-26.1)	<4 (<7.0)	239 (4.2)	0.7 (0.2-3.3)
Parathyroid	E20-E21	252	0 (0)	18 (0.2)	NA	<4 (<7.0)	30 (0.5)	36.0 (1.3-972.1)
Mental and behavioral disorders	F	290-315	22 (21.4)	837 (8.1)	4.3 (2.2-8.4)	5 (8.8)	656 (11.5)	0.5 (0.2-1.5)
Intellectual disability	F70-79	310-315	6 (5.9)	34 (0.3)	5.0 (1.8-14.1)	4 (7.0)	9 (0.2)	40.0 (11.0-145.9)
Disorders of speech, language, and scholastic skills	F80-F81	30609-30619	<4 (<3.8)	4 (0.04)	2884.0 (188.4-44138.6)	0 (0)	<4 (<0.1)	NA
Behavioral and emotional disorders	F90-F98	30629-308	<4 (<3.8)	73 (0.7)	8.3 (1.3-51.6)	0 (0)	21 (0.4)	NA
Nervous system	G	320-358	17 (16.5)	853 (8.3)	3.2 (1.6-6.7)	10 (17.5)	752 (13.2)	1.3 (0.6-3.0)
Episodic and paroxymal disorders	G40-G47	345-346 34700-34709	12 (11.7)	445 (4.3)	4.8 (2.0-11.6)	5 (8.8)	340 (6.0)	1.3 (0.4-3.6)
Eye and adnexa	H00-H59	360-379	16 (15.5)	842 (8.2)	4.2 (1.9-9.4)	9 (15.8)	839 (14.7)	1.7 (0.8-3.6)
Disorders of refraction and accommodation	H52	370	<4 (<3.8)	85 (0.8)	7.5 (1.5-36.4)	<4 (<7.0)	63 (1.1)	1.5 (0.2-10.1)
Visual disturbances, blindness, and low vision	H53-H54	37729-37739 379	4 (3.9)	66 (0.6)	16.3 (3.5-75.1)	0 (0)	48 (0.8)	NA
Ear	H60-H95	380-389	16 (15.5)	775 (7.5)	3.1 (1.4-6.7)	5 (8.8)	531 (9.3)	0.6 (0.2-1.7)
Hearing loss	H90-H91	388-389	6 (5.9)	203 (2.0)	5.7 (1.7-18.5)	<4 (<7.0)	292 (5.1)	0.3 (0.1-1.4)
Circulatory system	I	390-458	19 (18.4)	1246 (12.1)	1.5 (0.9-2.7)	12 (21.1)	1853 (32.5)	1.3 (0.5-3.7)
Pulmonary embolism	I26	45099	<4 (<3.8)	42 (0.4)	12.2 (1.6-92.8)	0 (0)	57 (1.0)	NA
Venous thrombosis	I80-I82	451-453	7 (6.8)	187 (1.8)	6.1 (1.9-18.9)	<4 (<7.0)	261 (4.6)	0.5 (0.1-2.5)
Respiratory system	J	460-519	37 (35.9)	2440 (23.7)	2.1 (1.3-3.5)	18 (31.6)	1480 (26.0)	1.1 (0.5-2.4)
Pneumonia	J12-J18	480-486	13 (12.6)	590 (5.7)	2.2 (1.1-4.4)	4 (7.0)	523 (9.2)	0.8 (0.2-2.4)
Chronic lower respiratory disease	J40-J47	490-493, 518	10 (9.7)	641 (6.2)	2.8 (1.1-6.9)	4 (7.0)	430 (7.5)	0.6 (0.2-2.1)
Asthma	J45-J46	493	10 (9.7)	537 (5.2)	2.8 (1.1-6.8)	<4 (<7.0)	236 (4.1)	1.0 (0.2-4.8)
Oral cavity and gastrointestinal system	K	520-577	35 (34.0)	2288 (22.2)	2.8 (1.8-4.5)	19 (33.3)	1947 (34.2)	1.1 (0.5-2.5)
Diseases of hard tissue of teeth, including caries	K02-K03	521	5 (4.9)	78 (0.7)	11.5 (2.6-50.9)	<4 (<7.0)	36 (0.6)	3.2 (0.2-54.9)
Diseases of pulp and periapical tissues	K04	522	<4 (<3.8)	31 (0.3)	10.4 (2.0-52.8)	0 (0)	27 (0.5)	NA
Constipation	K590	56400, 56409	10 (9.7)	307 (3.0)	8.1 (3.0-21.7)	<4 (<7.0)	173 (3.0)	0.9 (0.2-4.5)

(continued)

Table 1 Continued

Diagnosis	ICD-10 Code	ICD-8 Code	Number of Females With 47,XXX (%)	Number of Controls (%)	IRR (95% CI)	Number of Females with 46,XX/ 47,XXX (%)	Number of Controls (%)	IRR (95% CI)
Cholelithiasis	K80	574	6 (5.8)	331 (3.2)	3.1 (1.2-7.8)	5 (8.8)	385 (6.8)	1.4 (0.5-3.8)
Skin and subcutaneous tissue	L00-L08	680-709	13 (12.6)	1029 (10.0)	1.6 (0.7-3.3)	12 (21.1)	768 (13.5)	3.3 (1.1-9.8)
Infections	L00-L08	680-686	8 (7.8)	428 (4.2)	2.5 (0.96-6.6)	7 (12.3)	302 (5.3)	6.8 (1.3-35.2)
Urticaria	L50	708	<4 (<3.8)	93 (0.9)	1.3 (0.2-6.8)	<4 (<7.0)	58 (1.0)	10.9 (1.2-97.6)
Musculoskeletal system and connective tissue	M	710-738	34 (33.0)	2667 (25.9)	1.8 (1.1-2.8)	27 (47.4)	2376 (41.7)	1.1 (0.8-1.7)
Osteoporosis	M80-M82	723	<4 (<3.8)	133 (1.3)	0.5 (0.1-3.1)	5 (8.8)	251 (4.4.)	3.8 (1.4-9.9)
Genitourinary system	N	580-629	24 (23.3)	2700 (26.2)	0.96 (0.6-1.5)	34 (59.6)	2563 (45.9)	2.1 (1.4-3.4)
Absent, scanty, and rare menstruation, including primary amenorrhea	N91	62600-62619	<4 (<3.8)	40 (0.4)	15.0 (2.8-79.9)	<4 (<7.0)	31 (0.5)	3.7 (0.2-67.6)
Habitual aborter	N96	NA	4 (3.8)	12 (0.1)	NA	9 (15.8)	13 (0.2)	112.6 (39.0-325.2)
Infertility	N97	628	4 (3.9)	351 (3.4)	1.2 (0.4-3.3)	12 (21)	327 (5.7)	4.1 (2.2-7.7)
Pregnancy and birth	O	630-677	33 (32.0)	3972 (38.6)	1.2 (0.8-1.7)	33 (57.9)	3187 (55.9)	1.4 (0.98-1.9)
Pregnancy with abortive outcome	O00-O08	640-645	22 (21.4)	1795 (17.4)	1.9 (1.2-3.1)	28 (49.1)	1424 (25.0)	3.7 (2.6-5.1)
Abortion, not induced	O00-O03	643-645	13 (12.6)	831 (8.1)	2.4 (1.4-4.3)	21 (36.8)	702 (12.3)	6.0 (4.1-8.9)
Maternal disorders predominantly related to pregnancy	O20-O29	630, 632-633 63470-63477 635-636 638-639	13 (12.6)	1010 (9.8)	2.4 (1.3-4.6)	18 (31.6)	750 (13.2)	2.0 (1.08-3.8)
Hemorrhage in early pregnancy	O20	632	6 (5.8)	420 (4.1)	2.2 (0.9-5.1)	13 (22.8)	413 (7.2)	2.8 (1.7-4.6)
Diabetes in pregnancy	O24	63474	5 (4.9)	95 (0.9)	4.9 (1.8-13.4)	0 (0)	5 (0.1)	NA
Disorders related to the perinatal period	P	760-779	26 (25.2)	1348 (13.1)	3.1 (1.5-6.8)	4 (7.0)	119 (2.1)	7.0 (2.3-21.5)
Congenital malformations and genetic disorders	Q	740-759	60 (58.3)	773 (7.5)	151.8 (81.3-283.3)	9 (15.8)	282 (4.9)	11.7 (2.6-51.8)
Eye, ear, face, neck	Q10-Q18	744-745	5 (4.9)	184 (1.8)	7.6 (1.4-41.0)	<4 (<7.0)	75 (1.3)	7.3 (1.9-28.8)
Malformations of ear, other	Q17	74519-74539	<4 (<3.8)	74 (0.7)	2.9 (0.6-13.5)	<4 (<7.0)	6 (0.1)	29.4 (2.3-165.8)
Circulatory system	Q20-Q28	746-747	8 (7.8)	110 (1.1)	356.1 (21.2-5978.3)	0 (0)	24 (0.4)	NA
Malformations of cardiac septae	Q21	74629-74639 74640-74649 74659	5 (4.9)	47 (0.5)	769.8 (31.4-18843.5)	0 (0)	9 (0.2)	NA
Respiratory system	Q30-Q34	748	<4 (<3.8)	21 (0.2)	64.4 (3.0-1380.2)	0 (0)	14 (0.2)	NA
Gastrointestinal	Q35-Q45	749-751	<4 (<3.8)	56 (0.5)	12.6 (0.3-556.1)	<4 (<7.0)	24 (0.4)	8.1 (0.2-339.4)
Cleft palate	Q35	74909	<4 (<3.8)	12 (0.1)	42.0 (5.2-341.5)	0 (0)	<4 (<0.1)	NA
Female genital organs	Q50-Q52, Q56-Q64	75200-75209 75250-75279 75281, 75283 75289-75299	<4 (<3.8)	25 (0.2)	115.0 (9.5-1395.8)	<4 (<7.0)	19 (0.3)	92.5 (5.2-1648.2)

(continued)

Table 1 Continued

Diagnosis	ICD-10 Code	ICD-8 Code	Number of Females With 47,XXX (%)	Number of Controls (%)	IRR (95% CI)	Number of Females with 46,XX/47,XXX (%)	Number of Controls (%)	IRR (95% CI)
Musculoskeletal system	Q65-Q79	754-756	10 (9.7)	291 (2.8)	9.4 (2.8-31.5)	<4 (<7.0)	86 (1.5)	2.7 (0.3-23.3)
Deformities of feet	Q66	75400-75409	<4 (<3.8)	78 (0.8)	17.3 (1.9-160.9)	<4 (<7.0)	86 (1.5)	18.9 (2.2-163.0)
Other congenital malformations	Q80-Q89	75709-75929 75969-75999	7 (6.8)	80 (0.8)	45.5 (8.3-249.3)	<4 (<7.0)	29 (0.5)	1.9 (0.2-23.2)
Chromosomal abnormalities	Q90-Q99	75930-75959	48 (46.6)	14 (0.1)	936.0 (377.8-2319.0)	<4 (<7.0)	4 (0.1)	47043.9 (829.1-2669336)
Symptoms and abnormal findings, not elsewhere classified	R	780-796	47 (45.6)	3606 (35.0)	2.8 (1.9-4.2)	25 (43.9)	2449 (43.0)	1.3 (0.8-2.2)
External causes of morbidity	S,T,V,X, Y	800-999	69 (67.0)	7277 (70.7)	1.4 (1.08-1.9)	39 (68.4)	4120 (72.3)	0.99 (0.7-1.3)

IRRs for chapters according to the ICD-10. According to ethics regulations, the exact number of cases with a given diagnosis is not provided if <4.
ICD-8, Eighth Revision of International Classification of Diseases; *ICD-10*, 10th Revision of International Classification of Diseases; *IRR*, incidence rate ratio; *NA*, not applicable.

Discussion

In this nationwide study of administrative, longitudinally collected data on hospital diagnoses and prescribed medications, females with 47,XXX and females with 46,XX/47,XXX had a significantly increased overall occurrence of hospital diagnoses but not of prescribed medications. Both females with 47,XXX and those with 46,XX/47,XXX had a significantly increased occurrence of a variety of specific diagnoses and medications. Assessed from the number of affected diagnoses and prescriptions, the 47,XXX karyotype was associated with the most severe comorbidity burden when compared with controls.

Diminished ovarian reserve and accelerated loss of ovarian function have long been casuistically reported in females with 47,XXX syndrome[4], and among 110 females incidentally diagnosed with 47,XXX in the United Kingdom Biobank study age at natural menopause was significantly lower than in females with a 46,XX karyotype.[11] Moreover, genetic screening of patients diagnosed with primary ovarian insufficiency (POI), showed a 47,XXX karyotype in up to nearly 4% of cases (range = 0.6%-3.8%),[12-15] thus higher than the prevalence of 47,XXX syndrome in the general population. In a recent study of girls and adolescents ($n = 15$) with 47,XXX syndrome, in which measurements of anti-Müllerian hormone (AMH) concentrations were used as biomarkers of ovarian reserve, AMH concentrations were significantly lower in females with 47,XXX syndrome than in controls. Moreover, for two-thirds of the adolescents, AMH levels were below the range of normal for age.[16] Very little research has, however, been conducted on the relationship between 47,XXX syndrome and POI or early menopause. In this study, females with 47,XXX had a significantly increased occurrence of hospital diagnoses related to absent, scanty, and rare menstruation and among both females with 47,XXX and those with 46,XX/47,XXX, hormone replacement therapy was significantly increased, thus supporting presence of an extra X chromosome as a strong risk factor for ovarian dysfunction.

Successful pregnancies of women with 47,XXX syndrome have been reported,[17] and in the UK Biobank study, females with 47,XXX syndrome had a similar number of pregnancies and no higher number of pregnancy loss than females with 46,XX.[11] In contrast, we previously reported that the proportion of females diagnosed with 47,XXX syndrome who become mothers are significantly reduced compared with controls.[18] In this study, 47,XXX and 46,XX/47,XXX were associated with a markedly increased occurrence of pregnancy with abortive outcomes and hemorrhage during early pregnancy. Moreover, we found a significantly increased occurrence of diagnoses of infertility and recurrent miscarriage in females with 46,XX/47,XXX compared with controls, however not in females with 47,XXX. We do not consider this as an expression of better fertility in females with 47,XXX than in females with 46,XX/47,XXX, but rather a consequence of the seemingly

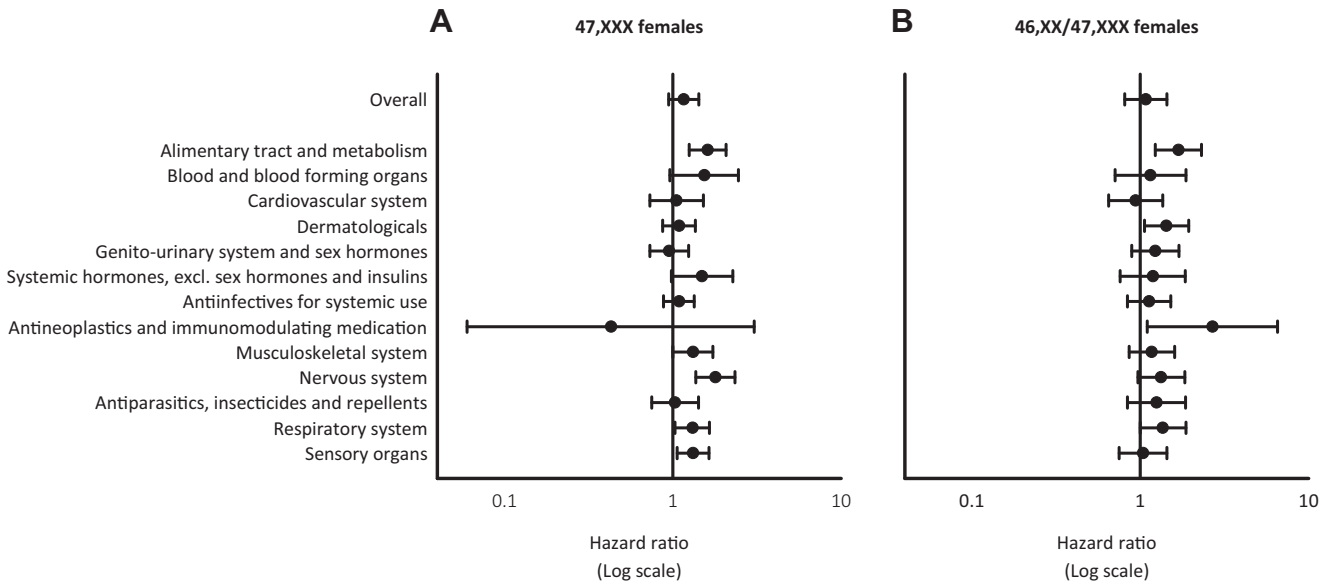

Figure 3 Prescribed medication in females with 47,XXX syndrome. Prescriptions are divided in chapters according to the Anatomical Therapeutic Chemical classification. In parentheses, the number of cases and controls having at least 1 record within the given chapter is shown. A. Females with 47,XXX. B. Females with 46,XX/47,XXX. excl., exclusive.

more severe phenotype in females with 47,XXX, which may reduce their likeliness to cohabitate and thus in turn reduce their likeliness to experience fertility and pregnancy problems. The significantly reduced use of contraceptives among females with 47,XXX supports this consideration. Recommendations for fertility counseling and preservation exist for patients at high risk for infertility, here among for patients with Turner syndrome, who are known to have rapidly decreasing ovarian reserve from a very young age.[19] Because far less information is available to assist health care providers in facilitating long-term discussions regarding this issue in 47,XXX syndrome, no such recommendations currently exist. Our findings underline the very importance of future studies to focus on fertility and the etiologies of infertility in patients with 47,XXX syndrome.

We found an increased occurrence of antiobesity prescriptions as well as of registrations of type 2 diabetes mellitus (DM2) and anti-diabetic prescriptions (except insulins) among females with 47,XXX. Ovarian dysfunction with early menopause or POI are well-known risk factors for developing metabolic syndrome and DM2 owing to a shorter exposure of endogenous estrogen, which may have a protective role on pancreatic β-cell function and insulin resistance.[20] Thus, we speculate whether the increased occurrence of obesity and DM2 in females with 47,XXX in this study indeed relates to an increased occurrence of ovarian dysfunction. Lifestyle factors such as dietary intake and exercise of course also play a central role in the development of DM2 and obesity. However, these cannot be accounted for in the current study. Another well-known, long-term effect of early menopause or POI is osteoporosis, and in this study, we found an increased risk of osteoporosis in females with 46,XX/47,XXX, whereas this was not the case in females with 47,XXX. The most likely explanation for this difference might be that females with 47,XXX were comparatively younger than females with 46,XX/47,XXX at the end of follow-up, and that the deleterious effects of hypogonadism on bone metabolism have not yet appeared.

It is well-known that autoimmune diseases are more likely to occur in patients with Turner and Klinefelter syndrome than in the general population,[21,22] and autoimmune mechanisms seem to be part of the underlying etiology in up to 30% of cases of POI.[23] Accordingly, based on a number of case reports of the coexistence of autoimmune disease, including autoimmune thyroid diseases, and POI in females with 47,XXX syndrome, autoimmunity has been suggested as the pathophysiological mechanism of ovarian dysfunction in 47,XXX syndrome.[12,24,25] It is also speculated whether autoimmune thyroid disorders could be analogous to that observed in Turner and Klinefelter syndrome.[12] This study revealed no association between 47,XXX syndrome and autoimmune diseases, neither when evaluating hospital diagnoses nor when evaluating prescribed medication (data not shown), and among those recorded with diagnoses potentially related to ovarian dysfunction, concomitance with a diagnosis of an autoimmune disease was observed in only 1 case. This study therefore does not support the hypothesis that females with a supernumerary X chromosome have a predisposition for autoimmune disease.

Sex chromosome trisomies are a risk factor for suboptimal neurodevelopment, including learning disabilities and impairment of language, social cognition, and executive function. Further, they present a risk factor for significant neurodevelopmental disorders such as autism spectrum disorders and attention deficit hyperactivity disorder.[26-28]

Table 2 Prescribed medication in 47,XXX syndrome

Medication	ATC Code	Number of 47,XXX (%)	Number of controls (%)	HR (95% CI)	Number of 46,XX/47,XXX (%)	Number of controls (%)	HR (95% CI)
Alimentary tract and metabolism	A	62 (60.2)	5087 (49.4)	1.6 (1.2-2.1)	40 (70.2)	3663 (64.3)	1.7 (1.2-2.3)
Stomatological preparations	A01	30 (29.1)	1995 (19.4)	1.7 (1.2-2.4)	9 (15.8)	991 (17.4)	1.04 (0.5-2.0)
Caries prophylactic agents	A01AA	9 (8.7)	211 (2.0)	4.9 (2.5-9.7)	0 (0)	139 (2.4)	NA
Corticosteroids	A01AC	4 (3.9)	136 (1.3)	3.1 (1.1-8.4)	<4 (<7.0)	110 (1.9)	2.1 (0.5-8.7)
Acid related disorders	A02	35 (34.0)	2312 (22.4)	2.1 (1.5-3.0)	23 (40.4)	2518 (44.2)	1.4 (0.9-2.1)
Functional gastrointestinal disorders	A03	23 (22.3)	1527 (14.8)	2.0 (1.3-3.0)	18 (31.6)	1306 (22.9)	1.8 (1.1-2.9)
Antiemetics	A04	<4 (<3.9)	139 (1.3)	1.7 (0.4-6.8)	4 (7.0)	102 (1.8)	4.4 (1.6-12.0)
Drugs for constipation	A06	15 (14.6)	649 (6.3)	3.2 (1.9-5.3)	11 (19.3)	620 (10.9)	2.9 (1.6-5.3)
Antiobesity preparations	A08	12 (11.7)	703 (6.8)	2.0 (1.1-3.5)	10 (17.5)	791 (13.9)	1.5 (0.8-2.7)
Antidiabetics	A10	8 (7.8)	276 (2.7)	3.3 (1.6-6.7)	4 (7.0)	329 (5.8)	1.4 (0.5-3.8)
Blood glucose lowering drugs, excl. Insulins	A10B	7 (6.8)	224 (2.2)	3.6 (1.7-7.7)	4 (7.0)	295 (5.2)	1.6 (0.6-4.2)
Blood and blood forming organs	B	18 (17.5)	1380 (13.4)	1.5 (0.96-2.5)	17 (29.8)	1713 (30.1)	1.2 (0.7-1.9)
Antithrombotic agents	B01	10 (9.7)	589 (5.7)	2.0 (1.05-3.7)	10 (17.5)	957 (16.8)	1.2 (0.6-2.3)
Cardiovascular system	C	29 (28.2)	3291 (32.0)	1.1 (0.7-1.5)	29 (50.9)	3331 (58.4)	0.9 (0.6-1.4)
Dermatologicals	D	78 (75.7)	8193 (79.5)	1.1 (0.9-1.4)	43 (75.4)	4303 (75.5)	1.4 (1.1-1.9)
Genito-urinary system and sex hormones	G	57 (55.3)	5892 (57.2)	0.95 (0.7-1.2)	38 (66.7)	3820 (67.0)	1.2 (0.9-1.7)
Hormonal contraceptives, systemic	G03A	38 (36.9)	4868 (47.3)	0.7 (0.5-0.9)	23 (40.4)	2407 (42.2)	1.1 (0.7-1.7)
Estrogens	G03C	12 (11.7)	831 (8.1)	1.7 (0.97-3.0)	17 (29.8)	1151 (20.2)	1.8 (1.1-2.9)
Progestogens	G03D	12 (11.7)	718 (7.0)	2.0 (1.1-3.5)	13 (22.8)	599 (10.5)	2.8 (1.6-4.8)
Progestogens and estrogens in combination	G03F	11 (10.7)	391 (3.8)	3.2 (1.7-5.8)	12 (21.1)	498 (8.7)	3.8 (1.9-6.0)
Gonadotropins and other ovulation stimulants	G03G	4 (3.9)	442 (4.3)	1.0 (0.4-2.7)	10 (17.5)	316 (5.5)	4.1 (2.2-7.7)
Systemic hormones, except sex hormones and insulins	H	22 (21.4)	1863 (18.1)	1.5 (0.98-2.3)	20 (35.1)	1826 (32.0)	1.2 (0.8-1.8)
Antiinfectives for systemic use	J	93 (90.3)	9487 (92.1)	1.1 (0.9-1.3)	46 (80.7)	5038 (88.4)	1.1 (0.8-1.5)
Antineoplastics and immunomodulating medication	L	<4 (<3.9)	275 (2.7)	0.4 (0.06-3.0)	5 (8.8)	215 (3.8)	2.7 (1.1-6.5)
Musculoskeletal system	M	52 (50.5)	5012 (48.7)	1.3 (0.99-1.7)	41 (71.9)	4110 (72.1)	1.2 (0.9-1.6)
Anti-inflammatory and anti-rheumatic products	M01	52 (50.5)	4934 (47.9)	1.4 (1.04-1.8)	41 (71.9)	4033 (70.8)	1.1 (0.8-1.6)
Pain, topical products	M02	<4 (<3.9)	199 (1.9)	1.8 (0.6-5.6)	7 (12.3)	226 (4.0)	4.2 (2.0-9.0)
Nervous system	N	55 (53.4)	4481 (43.5)	1.8 (1.4-2.3)	38 (66.7)	3877 (68.0)	1.3 (0.97-1.8)
Anesthetics	N01	<4 (<3.9)	140 (1.4)	1.6 (0.4-6.4)	<4 (<7.0)	63 (1.1)	6.1 (1.9-19.6)
Analgetics	N02	39 (37.9)	3308 (32.1)	1.7 (1.2-2.3)	34 (64.9)	3145 (55.2)	1.6 (1.1-2.2)
Opioids	N02A	29 (28.2)	1983 (19.3)	2.0 (1.4-2.9)	28 (49.1)	2202 (38.6)	1.7 (1.2-2.5)
Antiepileptica	N03	9 (8.7)	506 (4.9)	2.2 (1.1-4.2)	6 (10.5)	494 (8.7)	1.3 (0.6-2.8)
Anti-Parkinson medication	N04	5 (4.9)	171 (1.7)	3.9 (1.6-9.6)	<4 (<7.0)	239 (4.2)	0.5 (0.1-3.4)
Psycholeptica	N05	27 (26.2)	2127 (20.7)	1.5 (1.00-2.1)	24 (42.1)	2196 (38.5)	1.4 (0.94-2.1)
Antipsychotica	N05A	12 (11.7)	563 (5.5)	2.8 (1.6-5.0)	<4 (<7.0)	517 (9.1)	0.7 (0.2-2.1)
Hypnotica and sedatives	N05C	15 (14.6)	1217 (11.8)	1.4 (0.8-2.3)	20 (35.1)	1387 (24.3)	1.9 (1.2-3.0)
Psychoanaleptica	N06	30 (29.1)	1856 (18.0)	2.2 (1.5-3.2)	15 (26.3)	1644 (28.8)	1.1 (0.6-1.8)
Antidepressives	N06A	27 (26.2)	1785 (17.3)	2.1 (1.4-3.0)	15 (26.3)	1621 (28.4)	1.1 (0.6-1.8)
Agents used for ADHD and nootropics	N06B	4 (3.9)	157 (1.5)	2.9 (1.07-7.8)	0 (0)	46 (0.8)	NA
Antiparasitics, insecticides and repellents	P	38 (36.9)	4034 (39.2)	1.03 (0.7-1.4)	25 (43.9)	2319 (40.7)	1.2 (0.8-1.9)
Respiratory system	R	71 (68.9)	6920 (67.2)	1.3 (1.03-1.7)	40 (70.2)	3934 (69.0)	1.4 (0.99-1.9)

(continued)

Table 2 Continued

Medication	ATC Code	Number of 47,XXX (%)	Number of controls (%)	HR (95% CI)	Number of 46,XX/47,XXX (%)	Number of controls (%)	HR (95% CI)
Cough and cold preparation	R05	38 (36.9)	2655 (25.8)	2.0 (1.4-2.7)	26 (45.6)	2395 (42.0)	1.4 (0.9-2.1)
Antihistamines for systemic use	R06	40 (38.8)	3249 (31.5)	1.5 (1.1-2.1)	22 (38.6)	1956 (34.3)	1.5 (0.99-2.3)
Sensory organs	S	83 (80.6)	7677 (74.5)	1.3 (1.06-1.6)	36 (63.2)	3873 (67.9)	1.04 (0.7-1.4)
Ophthalmologicals	S01	80 (77.7)	7225 (70.1)	1.3 (1.1-1.7)	36 (63.2)	3640 (63.9)	1.1 (0.8-1.6)
Anti-infectives, eye	S01A	75 (72.8)	6649 (64.6)	1.3 (1.03-1.6)	33 (57.9)	3129 (54.9)	1.3 (0.9-1.8)
Antiglaucoma	S01E	<4 (<3.9)	102 (1.0)	1.3 (0.2-9.1)	4 (7.0)	148 (2.6)	3.3 (1.2-9.0)
Mydriatics and cycloplegics	S01F	4 (3.9)	136 (1.3)	3.3 (1.2-9.0)	0 (0)	61 (1.1)	NA
Decongestants and antiallergics	S01G	22 (21.4)	1610 (15.6)	1.6 (1.04-2.4)	10 (17.5)	1122 (19.7)	1.0 (0.5-1.9)
Otologicals	S02	18 (17.5)	1311 (12.7)	1.5 (0.96-2.4)	5 (8.8)	512 (9.0)	1.1 (0.4-2.6)
Anti-infectives	S02A	11 (10.7)	573 (5.6)	2.1 (1.2-3.8)	<4 (<7.0)	125 (2.2)	0.9 (0.1-6.4)
Ophthalmologicals and otologicals	S03	24 (23.3)	1514 (14.7)	1.9 (1.2-2.8)	8 (14.0)	971 (17.0)	0.9 (0.5-1.8)
Corticosteroids and anti-infectives, combination	S03C	24 (23.3)	1504 (14.6)	1.9 (1.2-2.8)	8 (14.0)	945 (16.6)	0.9 (0.5-1.9)
Various	V	0 (0)	106 (1.0)	NA	0 (0)	70 (1.2)	NA

HRs for chapters according to the ACT. According to ethics regulations, the exact number of cases with a given diagnosis is not provided if <4.
ADHD, attention deficit hyperactivity disorder; *ATC*, Anatomical Therapeutic Chemical System; *HR*, hazard ratio; *NA*, not applicable.

Thus, not surprisingly, we found an increased occurrence of diagnoses of intellectual disability among females with 47,XXX and 46,XX/47,XXX. Among females with 47,XXX we also found an icreased occurence of development disorders of speech, language, and scholastic skills as well as of diagnoses related to behavioral and emotional disorders. In addition, 47,XXX was associated with an increased risk of prescriptions for attention deficit hyperactivity disorder as well as for prescriptions of antipsychotics and antidepressives. Clinical studies show that the neurodevelopmental profile in 47,XXX syndrome is highly variable and perhaps depending on whether the diagnosis is obtained prenatally or postnatally because a number of studies have reported a tendency toward improved outcomes in prenatally ascertained cases.[8,29-31] We speculate whether such difference is due to more patients being incidentally diagnosed in the prenatal setting, eg, owing to screening because of advanced maternal age, and thus more likely to belong to the group of females with 47,XXX who are asymptomatic or who present with only subtle symptoms compared with patients diagnosed in a postnatal setting, where, eg, cognitive and developmental concerns may be the primary cause for performing a chromosome analysis. In addition, prenatal diagnosis allows for follow-up and timely intervention whenever delays are recognized.[8] Nevertheless, in a newly published study on social functioning and emotion recognition in adults with 47,XXX syndrome, no significant differences between prenatally (n = 10) and postnatally (n = 24) diagnosed cases were observed.[32] Owing to the rise in prenatal genetic testing, the demand for accurate and comprehensive counseling regarding expected outcomes will increase, and there is a need for future studies of large prenatally ascertained cohorts.

A variety of minor and major malformations have been reported in association with 47,XXX syndrome with most malformations affecting the urogenital system.[6,29] In this study, the 47,XXX karyotype was associated with a significantly increased occurrence of malformations within virtually every organ system, and nearly 8% were registered with a malformation of the circulatory system. Interestingly, previous studies have reported that heart anomalies in females with 47,XXX syndrome are rare and do not exceed the population prevalence of 0.8%.[4] With regard to malformations of the urinary system and female genital organs, both females with 47,XXX and those with 46,XX/47,XXX were found to be significantly affected, however, we detected no clear pattern of anomalies, probably owing to the limited number of cases.

We found a significantly increased occurrence of diagnoses of pneumonia and asthma in females with 47,XXX. Previously, in an epidemiological study of mortality in 47,XXX syndrome, a 4-fold increased mortality associated with respiratory diseases was reported,[10] and in a clinical study evaluating associated medical conditions among 74 girls, adolescents, and young women with 47,XXX syndrome, nearly one-fourth had asthma.[8] Interestingly, similar findings have been reported for both Klinefelter and

47,XYY syndrome.[33,34] Thus, it appears that sex chromosome trisomies in some way increases susceptibility to respiratory disease. In this study, unfortunately, we have no information regarding smoking habits.

Gastrointestinal symptoms, including gastroesophageal reflux, constipation, and abdominal pain, have for long been a concern in 47,XXX syndrome.[8,17] Our study supports this concern because both females with 47,XXX and those with 46,XX/47,XXX had a significantly increased risk of being prescribed a variety of medications related to such symptoms, and among females with 47,XXX there was a significant increased risk of being registered with a diagnosis of obstipation. However, we did not detect an increased risk of specific gastrointestinal disorders that could serve as underlying organic pathology.

Dental problems and a reduction in craniofacial growth with reduced overall length of the calvaria, the anterior and posterior cranial bases, and the facial complex have been described in 47,XXX syndrome.[8,35] Among females with 47,XXX, we found an increased risk of diseases related to the hard tissue of the teeth and to the periapical tissues combined with an increased occurrence of caries prophylactic prescriptions. This emphasizes that oral health is another aspect of the 47,XXX syndrome to be aware of in the clinical follow-up of these patients.

Epilepsy is a common finding in persons with chromosome aberrations, and epilepsy/seizure disorders and electroencephalography abnormalities have been described for a number of females with 47,XXX syndrome.[36] In the previously mentioned study by Wigby et al,[8] 16% of cases were reported to have a seizure disorder, with the majority of cases being postnatally ascertained. This study supports a link between the presence of a supernumerary X chromosome and seizure disorders since females with 47,XXX had a significantly increased occurrence of diagnoses of episodic and paroxysmal disorders and an increased occurrence of antiepileptic prescriptions.

We found a significantly increased risk of thrombophilia, venous thrombosis, and pulmonary embolism among females with 47,XXX combined with a significantly increased risk of being prescribed antithrombotic medication. Previously, we have observed a similar pattern in both Klinefelter and 47,XYY syndrome[33,37] and among males with Klinefelter syndrome, who per definition suffer from hypergonatrophic hypogonadism, we have described an insignificantly inverse association between testosterone treatment and venous thrombosis and thrombotic deaths.[37] Interestingly, in this study, 7 of 9 cases who were registered with a diagnosis of either venous thrombosis or pulmonary embolism were prescribed contraceptives for systemic use, corresponding to nearly 20% (7/38) of all cases receiving hormonal contraceptives. We speculate whether the extra X chromosome contributes to an underlying alteration in the coagulation system toward a prothrombotic state and whether more caution should be paid when deciding which contraceptive treatment to offer. Further studies should be undertaken to evaluate thrombosis risk in 47,XXX syndrome.

Mosaicism constitutes a major challenge for prediction of outcome in sex chromosome abnormalities, like in all other genetic conditions, because the outcome may depend on both the degree of mosaicism as well as on which tissues are affected. In this study, females with 46,XX/47,XXX were less severely affected overall than females with 47,XXX based on the assessment of the number of significantly affected diagnoses and prescribed medication, which is in line with previous reports.[2]

Strengths and limitations

The present study has both advantages and drawbacks to consider when interpreting the results. Most literature on 47,XXX syndrome is dominated by case reports or small single-center cross-sectional clinical studies in which both ascertainment bias and recruitment bias limit the ability to generalize findings to unselected cohorts. Epidemiological studies allow for studying much larger cohorts and are by design exempt from survivor bias. In this study, we present data for a nationwide cohort of females with 47,XXX and females with 46,XX/47,XXX and thus the study cohort can be considered complete. However, as most females with 47,XXX syndrome remain undiagnosed,[9] it is of utmost importance to be aware that results from the current study not necessarily may be applicable to those females. Indeed, they may remain undiagnosed owing to presentation of an either completely normal or just very mildly affected phenotype not meeting the threshold for genetic testing. Only screening of very large cohorts or even an entire population will enable us to shed light on this intriguing enigma. Nevertheless, the females with 47,XXX and females with 46,XX/47,XXX who are presented here represent those whom clinicians know from the daily clinic. With the increasing use of prenatal diagnostics, it is, however, likely that we will experience an increase in incidentally diagnosed females with 47,XXX and females with 46,XX/47,XXX for whom the results from the current study may not necessarily be extrapolatable to. This is especially important to be aware of in the prenatal setting in which expecting parents may face a dilemma of whether to continue the pregnancy or not.

Use of genetic screening in diagnostic work-ups is rapidly increasing, and for conditions such as sex chromosome abnormalities, in which the phenotypic spectrum is very broad, it is becoming more common to search for a secondary genetic diagnosis in case of severe features.[38] Because the registries only include cytogenetic data, we are unable to account for cases in which an additional genetic diagnosis may have been found, but because most cases included in the study were diagnosed at a time when additional genetic analyses were not available, we believe that this only affects very few, if any at all. Conversely, we

also cannot account for this among controls, and hence, an eventual impact on data will be limited.

Epidemiological studies are excellent for providing information on specific comorbidity patterns in relation to the specific condition in question,[39] and the current constellation of universal tax-funded health care combined with lifelong registration of health events in highly valid registries, is a major strength of the current study. Furthermore, the possibility of accurate individual-level linking of data from different registries, enable us to use data on specific medications to improve the comorbidity pattern gleaned by hospital diagnoses, although we are unable to directly link prescriptions and indication for treatment. The use of medication data further allows us to identify and draw more precise conclusions on diseases that often do not lead to a hospital encounter because often managed by general practitioners (eg, mild depression/anxiety and DM2).

Conclusion

This nationwide study of hospital diagnoses and prescribed medications in an unselected cohort of females diagnosed with a 47,XXX or 46,XX/47,XXX karyotype shows that the presence of a supernumerary X chromosome is related to a significantly increased comorbidity burden attributable to a wide selection of medical, psychiatric, and neurodevelopmental conditions. Overall, non-mosaic females with 47,XXX are more severely affected than those also presenting with a 46,XX cell line. The study does not allow us to draw any firm conclusions regarding the specific mechanisms for this increased comorbidity. However, whereas some diseases may be a direct effect of the extra X chromosome, others may be an indirect effect of a generally poorer health status, subsequent to an inferior socioeconomic status.[18] The wide spectrum of associated risks underlines the need for a specialized multidisciplinary approach toward females with 47,XXX syndrome to improve long-term outcomes. We therefore recommend follow-up of all females who receive a diagnosis of 47,XXX syndrome.

Data Availability

Data access requires authorization by Statistics Denmark (www.dst.dk) and approval from the Danish Cytogenetic Central Registry (www.auh.dk/afdelinger/klinisk-genetisk-afdeling/til-fagfolk/dccr/) and the Danish Data Protection Agency (www.datatilsynet.dk).

Acknowledgments

The study was financially supported by research grants from The Novo Nordisk Foundation (NNF15OC0016474, NNF20OC0060610), the Familien Hede Nielsens Foundation, and the Health Research Foundation of Central Denmark Region. C.H.G., A.B., and K.S. are members of the European Reference Network on Rare Endocrine Conditions (Endo-ERN), project identification number 739543.

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Ethics Declaration

The project was approved by the Danish Cytogenetic Central Registry and the Danish Data Protection Authority (journal number: 2013-41-2017). According to Danish law, the study needed no ethics committee approval and data from the registries were collected without patient consent.

Conflict of Interest

The authors declare no conflicts of interest.

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