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Morbidity in Klinefelter Syndrome: A Danish Register Study Based on Hospital Discharge Diagnoses

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Background: Klinefelter syndrome (KS) is the most prevalent sex chromosome disorder in man; it affects approximately one in 660 men and is a common cause of hypogonadism and infertility. Our current knowledge of morbidity in KS is based on observational studies and case reports and therefore is limited.

Design: We used Danish registers to obtain dates of hospital admissions and discharge diagnoses in a cohort of all males diagnosed with KS in Denmark and a randomly selected, age-matched control group. Our cohort consisted of 832 KS subjects and 4033 control subjects, contributing with a total of approximately 100,000 person years. We used stratified Cox regression analysis on main groups of diagnoses. Where significant results were found, subsequent analyses were performed on subgroups of diagnoses.

Results: We found a significantly increased risk of being hospitalized among the KS subjects [hazard ratio (HR), 1.69; 95% confidence interval, 1.54–1.86]. The increased admission risk was present in all but one of the main diagnosis groups, with the highest HRs for congenital malformations (HR, 10.7), psychiatric disorders (HR, 3.7), and endocrine and metabolic disorders (HR, 3.2). We compared hospitalization rates before and after the diagnosis of KS and found that the increased rate was present even before the diagnosis of KS.

Conclusions: Males suffering from KS experienced an increased hospitalization rate from a variety of disorders. Some are likely to be caused by hypogonadism, and some may be linked to the syndrome *per se*, whereas others are not readily explained. However, other factors, *e.g.* socioeconomic, may be involved. **(*J Clin Endocrinol Metab* 91: 1254–1260, 2006)**

KLINEFELTER SYNDROME (KS) is the most frequent sex chromosomal disorder, affecting approximately one in every 660 males (1, 2). It is characterized by the presence of one or more extra X-chromosomes, with the karyotype 47,XXY being the most prevalent type.

The prototypical man suffering from KS has traditionally been described as tall, with narrow shoulders, broad hips, sparse body hair, small testicles, lower intelligence, and androgen deficiency (3). Recently, a less well-defined phenotype has been recognized, presenting with fewer stigmata compared with the prototype (4).

Our knowledge of morbidity or comorbidity in KS is largely based on small-scale observational studies, cross-sectional studies, or case reports. These studies may all suffer from selection problems, because they typically describe the prevalence of a specific disease or biochemical marker of disease in a population of known KS patients. They point toward an increased incidence of osteoporosis (5–7), breast cancer (8, 9), mediastinal tumors (10), mitral valve prolapse (11), glucose intolerance and diabetes mellitus (12), thromboembolic diseases (13), retention of the testes (14), and autoimmune/rheumatologic diseases (15), particularly systemic lupus erythematosus (SLE) (16).

Two previous studies of mortality (the ultimate consequence of morbidity) in KS showed an increased risk of dying from lung cancer, breast cancer, diabetes mellitus, circulatory diseases, nonischemic heart disease, cerebrovascular disease, respiratory disease, and vascular insufficiency of the intestine (17, 18). We recently found an increased risk of dying from infectious, neurological, circulatory, pulmonary, and urinary tract diseases using the same cohort as in the present study (19).

In this report we describe morbidity as expressed by hospitalizations in KS using three registers covering the Danish nation.

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Abbreviations: CI, Confidence interval; HR, hazard ratio; KS, Klinefelter syndrome; SLE, systemic lupus erythematosus.

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Subjects and Methods

The registers

We created a cohort of KS subjects from the Danish Cytogenetic Central Register. We subsequently used discharge diagnoses from the National Register of Patients to describe the morbidity in all the males diagnosed with KS in Denmark compared with an age-matched control group drawn randomly from the Danish Civil Register.

The Danish Civil Registration System has, since 1968, allocated a unique personal identification number to each person living in Denmark, and it records information on emigration and deaths. The personal identification number is used for a number of administrative purposes and is included in a number of registers, thus giving unique opportunity for record linkage.

The Danish Cytogenetic Central Register has recorded all cytogenetic examinations performed in Denmark, both prenatal and postnatal, since 1960. The register includes information on karyotype and date of diagnosis and contains approximately 200,000 cytogenetic examinations; of these, 160,000 are prenatal, and 40,000 are postnatal examinations. The annual number of examinations is approximately 10,000. It is important to stress that the register only contains information regarding karyotype

and no information regarding phenotype. The reasons for performing karyotype examinations have been described previously (20).

The National Register of Patients has, since 1977, recorded discharge diagnoses for all patients admitted to public hospitals in Denmark. The public hospital system covers nearly all somatic admissions in Denmark, leaving a few admissions (mainly elective surgery) for private clinics and hospitals. During the years 1977–1993 International Classification of Diseases revision 8 (ICD-8) was used, and since 1994 International Classification of Diseases revision 10 (ICD-10) was used. For each discharge, a primary diagnosis and one or more secondary diagnoses were recorded.

The cohort

From the Danish Cytogenetic Central Register we created a cohort based on all 859 males diagnosed with KS. Twenty-four of these were excluded because they died or emigrated before January 1, 1977, when the National Register of Patients started. We also excluded three subjects who were diagnosed postmortem. An age- and calendar time-matched control cohort was created from the Danish Civil Register by extracting five randomly selected men, matched by month and year of birth, for each of the 832 KS subjects (4160 men). We had to exclude 84 control subjects because they died before January 1, 1977, and 43 control subjects who died before the diagnosis of KS in their matching KS subject. This was done to ensure comparability between the groups, because KS subjects dying before the diagnosis of KS for obvious reasons could not be included. The final cohort consisted of 4865 subjects (832 KS subjects and 4033 control subjects). Of these, 3543 were admitted to hospital during the period investigated (709 KS subjects and 2834 control subjects).

Information on vital status (alive, dead, emigrated, or disappeared) as well as dates of the event were also extracted from the Danish Civil Register. Time at risk started at the date of birth or January 1, 1977, whichever came last, for both the KS subjects and their matching controls. Censoring of individuals took place on December 31, 2001, or at the time of death, emigration, or disappearance, whichever came first.

Information on dates of admittance and discharge diagnoses was obtained from the National Register of Patients.

Statistical analysis

Hazard ratios (HRs) were calculated using Cox regression analysis with stratification, using each KS subject and his matched control subjects as a stratum. The matching ensured that comparisons were adjusted for age and calendar time.

HRs for first-time admissions were calculated for each of 16 ICD-10 chapters; ICD-8 diagnoses were translated to the corresponding ICD-10 chapter. If a significant HR was found in an ICD-10 chapter, subsequent analyses of diagnosis subgroups were performed. As an example, the HR for chapter 4 diseases (endocrine and metabolic diseases) was significantly elevated. Analyses of subgroups (diabetes, thyroid diseases, *etc.*) were performed. HRs for specific diagnoses of interest (*e.g.* intestinal thrombosis) based on previous reports were also calculated.

We did not distinguish between primary and secondary diagnoses; for each person a diagnosis was only included the first time it occurred, regardless of whether it was a primary or secondary diagnosis. Subsequent admissions with the same diagnosis were not included in the analysis.

To determine the effect of the KS diagnosis on the admission rate, we also calculated HRs on chapter levels, before and after the date of KS diagnosis.

All results are shown with 95% confidence intervals (CI). We made no formal corrections for multiple testing, but we avoided analysis of subgroups of diagnoses, unless there was a significant difference at a more aggregate level.

Intercooled Stata 8.2 for Windows (Stata Corp., College Station, TX) was used for all calculations.

The study was approved by The Danish Data Protection Agency and the involved registers.

Results

The general first-admission rate was significantly elevated for KS subjects compared with controls (HR, 1.69; 95% CI, 1.54–1.86; $P < 0.001$).

Dividing diagnoses into 16 groups (ICD-10 chapters), the first-admission rate was significantly increased for all 16, except for one chapter (diseases in the newborn; Fig. 1). By further subdividing these chapters, it was possible to describe the morbidity in more detail (Table 1). We also analyzed the frequency of specific diagnoses based on previous reports; these results are listed in Table 2 whether significant or not.

Summary of results

Infections. There was no demonstrable increase or decrease in any subdiagnoses.

Cancer. Breast cancer and mediastinal tumors were more frequent among KS subjects.

Blood diseases. Anemia was more frequent among KS subjects.

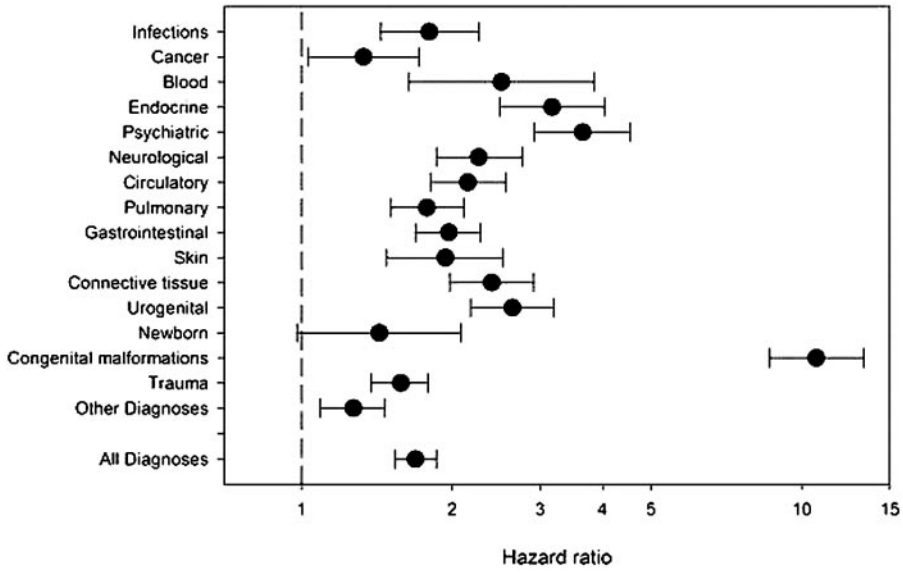

FIG. 1. HRs with 95% CI for diagnosis groups and for all diagnoses.

TABLE 1. HRs for first admission to hospital: all diagnoses, diagnosis chapters, and some subgroups of diagnoses (only significant subgroup-diagnoses are shown)

Disease	ICD-10 codes	ICD-8 codes	KS subjects	Control subjects	HR (95% CI)
Subjects in cohort			832	4033	
All diagnoses	A00-Z99	000–999	709	2834	1.69 (1.54–1.86)
Infections	A00-A99	000–136	108	313	1.80 (1.44–2.26)
Cancer	C00-D48	140–239	79	343	1.33 (1.03–1.72)
Blood diseases	D50-D89	280–289	38	71	2.51 (1.64–3.84)
Anemia	D50-D64	280–285	23	38	3.15 (1.73–5.76)
Endocrine diseases	E00-E90	240–279	122	209	3.17 (2.49–4.03)
Hypothyroidism	E00+E03	243–244	6	2	27.4[a]
Diabetes	E10-E14	250	49	105	2.30 (1.61–3.29)
Type 1	E10		15	33	2.21 (1.18–4.14)
Type 2	E11		25	38	3.71 (2.14–6.40)
Hypogonadism	E29	257.19–257.99	28	1	119 (16.2–880)
Psychiatric diseases	F00-F99	290–315	145	230	3.65 (2.92–4.55)
Psychoses	F20-F29	290–299	22	28	4.97 (2.68–9.22)
Neuroses/disorders of personality	F40-F48	300–309	93	141	3.54 (2.69–4.65)
Mental retardation	F80-F89	310–315	35	7	26.9 (11.3–64.1)
Neurological diseases	G00-G99	320–389	153	370	2.26 (1.86–2.76)
Cerebral palsy/paresis	G80-G83	343–344	12	22	2.89 (1.37–6.13)
Epilepsies	G40	345	46	53	4.28 (2.86–6.41)
Eye disorders	H00-H59	360–369	29	38	4.46 (2.65–7.53)
Circulatory diseases	I00-I99	390–458	211	622	2.15 (1.81–2.56)
Ischemic heart disease	I20-I25	410–414	72	229	1.71 (1.28–2.29)
Thrombophlebitis and thrombosis of the veins	I80.0–I80.9	451	39	41	5.29 (3.29–8.50)
Pulmonary embolism	I26	450	19	26	3.60 (1.92–6.74)
Pulmonary diseases	J00-J99	460–519	201	603	1.78 (1.51–2.11)
Pneumonia	J13-J15	480–486	65	129	2.95 (2.15–4.06)
Chronic obstructive pulmonary disease	J40-J43	490–492	40	64	3.89 (2.50–6.07)
Asthma	J45-J46	493	32	54	3.29 (2.09–5.18)
Gastrointestinal diseases	K00-K93	520–577	261	724	1.97 (1.69–2.28)
Ulcer	K25-K27	531–533	27	78	1.70 (1.08–2.68)
Cirrhosis of the liver	K74+K70.3	571	12	22	2.75 (1.33–5.68)
Skin diseases	L00-L99	680–709	80	205	1.94 (1.48–2.53)
Skin infections	L00-L08	680–686	42	137	1.52 (1.07–2.16)
Eczema and bullous disorders	L10-L30	690–695	11	21	2.30 (1.07–4.93)
Diseases of the musculoskeletal system and connective tissue	M00-M99	710–738	166	394	2.40 (1.98–2.91)
Osteoarthritis	M15-M19	713	38	58	4.46 (2.82–7.06)
Diseases of the urogenital system	N00-N99	580–629	175	375	2.64 (2.18–3.20)
Infections	N10-N12+N30	590+595	24	35	3.62 (2.09–6.26)
Gynecomastia	N62.9	611.11	37	6	34.8 (13.7–88.6)
Diseases in the newborn	P00-P96	760–780	35	119	1.42 (0.98–2.08)
Congenital malformations (including KS)	Q00-Q99	740–759	276	144	10.7 (8.63–13.3)
Heart	Q20-Q28	746–747	13	14	4.71 (2.18–10.2)
Genitalia	Q50-Q56	752	49	45	5.17 (3.45–7.75)
Retention of the testis	Q53	752.10–752.19	43	33	6.25 (3.97–9.84)
Trauma and intoxications	S00-T98	800–999	324	1114	1.58 (1.38–1.79)
All fractures	S02+S12+ S22+S32+ S42+S52+ S62+S72+ S82+S92	800–829	135	474	1.41 (1.16–1.72)
Other diagnoses (Z-/Y-diagnoses)	Z00-Z99	Y-diagnoses	231	915	1.27 (1.09–1.47)

ICS, International Classification of Diseases.
[a] Due to too few informative strata, CIs are omitted.

Endocrine and metabolic diseases. Hypothyroidism, all types of diabetes combined, type 1 and type 2 diabetes separately, obesity, as well as hypogonadism were all significantly more frequent among KS subjects.

Psychiatric disorders. Psychoses, neuroses/disorders of personality and mental retardation were all significantly more frequent among KS subjects.

Neurological diseases. Cerebral palsy/paresis, epilepsy, and eye diseases were all significantly more frequent among KS subjects.

Circulatory diseases. Ischemic heart disease, thrombosis of the deep veins, pulmonary embolism, and intestinal thrombosis were all more frequent among KS subjects.

Pulmonary diseases. Pneumonia, chronic obstructive airway disease (nonasthmatic), and asthma were all more frequent among KS subjects.

Gastrointestinal diseases. Ulcer and cirrhosis of the liver were more frequent among KS subjects.

Skin diseases. Skin infections and eczema were more frequent among KS subjects.

TABLE 2. Diagnoses with specific interest due to previous findings

Disease	ICD-10 codes	ICD-8 codes	KS subjects	Control subjects	HR (95% CI)
Subjects in cohort			832	4033	
Breast cancer	C50	174	3	0	∞[a]
Mediastinal tumors	C38.1-C38.3	163.19	3	1	14.2[a]
Diabetes	E10-E14	250	49	105	2.30 (1.61–3.29)
Type 1	E10		15	33	2.21 (1.18–4.14)
Type 2	E11		25	38	3.71 (2.14–6.40)
Adipositas	E65 - E66		8	12	3.41 (1.34–8.66)
Thrombosis of the deep veins	I80.1–2		14	12	6.63 (2.86–15.4)
Pulmonary embolism	I26	450	19	26	3.60 (1.92–6.74)
Cerebrovascular disease	I60–I69	430–438	38	153	1.19 (0.78–1.81)
Intestinal thrombosis	K55	569.14	2	1	7.89[a]
Mitral valve prolapse	I34.1	424.01–424.09	4	8	2.37 (0.66–8.50)
Osteoporosis	M80-M82	723.9	6	6	8.01 (1.98–32.5)
Generalized rheumatologic diseases	M30-M36	716+734	3	10	1.67 (0.44–6.34)
Systemic lupus erythematosus	M32	734.19	1	1	4.47[a]
Osteoporotic fractures (spine, forearm, and hip)	S32+S52.2 -.6 S72.0-.2	805+820+ 813.21	31	73	2.24 (1.44–3.48)

ICD, International Classification of Diseases.
[a] Due to too few informative strata, CIs are omitted.

Bone and connective tissue diseases. Osteoarthritis, osteoporosis, and SLE were more frequent among KS subjects.

Diseases of the urogenital system. Urogenital infections and gynecomastia were more frequent among KS subjects.

Congenital malformations. Malformations of the heart and genitalia and retention of the testes were more frequent among KS subjects.

Trauma. All fractures and osteoporotic fractures (hip, spine, and distal forearm) were more frequent among KS subjects.

Admission risk before and after KS diagnosis

Table 3 shows the HRs before and after the diagnosis of KS. Before the KS diagnosis, all but three groups of diagnoses (infections, skin diseases, and other diagnoses) were significantly more frequent among KS subjects. After the KS diagnosis, all but cancer diagnoses were significantly more frequent.

TABLE 3. HRs for admission before and after the diagnosis of KS

Disease group	Before diagnosis of KS		After diagnosis of KS	
	HR	95% CI	HR	95% CI
All	1.58	1.42–1.73	1.77	1.54–2.03
Infections	1.34	0.93–1.91	2.29	1.73–3.01
Cancer	2.11	1.37–3.24	1.28	0.96–1.71
Blood	2.76	1.25–6.09	2.34	1.43–3.82
Endocrine	3.94	2.63–5.90	2.53	1.90–3.38
Psychiatric	5.10	3.58–7.27	3.03	2.29–4.00
Neurologic	1.88	1.40–2.54	2.27	1.77–2.90
Circulatory	1.80	1.41–2.31	2.00	1.65–2.42
Respiratory	1.48	1.16–1.90	1.75	1.42–2.16
Gastrointestinal	1.29	1.03–1.62	2.10	1.76–2.51
Skin	1.30	0.83–2.04	2.33	1.69–3.21
Musculoskeletal	1.97	1.44–2.70	2.41	1.93–3.00
Urogenital	2.06	1.50–2.83	2.72	2.17–3.42
Newborn	1.50	1.03–2.20	[a]	
Congenital malformations	8.31	6.23–11.1	14.2	10.2–19.7
Trauma	1.29	1.09–1.54	1.77	1.50–2.09
Other	1.00	0.83–1.20	1.74	1.37–2.21

[a] Due to few informative strata, statistical analysis was not possible.

Discussion

This is the first study systematically describing the morbidity in KS. We would like to point out that the aim of this study was descriptive rather than hypothesis testing. We therefore only present the diagnoses/groups of diagnoses where significantly increased risk was present, with the exception of the diagnoses previously described as being more common in KS. We made no formal corrections for multiple testing, and CIs should be interpreted with caution.

Generally, we found a 69% increased risk of being admitted to the hospital with any diagnosis. Admissions with almost all diagnosis groups were more frequent among the KS subjects than among the control subjects. When interpreting the data, one should consider that only a minority (25%) of men suffering from KS are diagnosed, and most of them are diagnosed in adulthood (2). The cause of the elevated risk of admittance may be due to the chromosome aberration itself, *i.e.* a gene-dose effect of noninactivated genes on the extra X-chromosome; an indirect effect of the extra X-chromosome, *i.e.* hypogonadism and later consequences of hypogonadism; and lastly, effects of non-X-chromosome-related impacts, *i.e.* socioeconomic status (which, of course, may be related to learning disabilities, psychiatric disturbances, *etc.*), if this can be seen independently of the chromosome aberration.

The gene-dose effect may be a plausible cause of the congenital malformations and testicular failure and may also account for the increased risk of delayed speech, learning difficulties, and psychiatric diseases. Disturbed lateralization of the brain hemispheres has been associated with aneuploid number of X-chromosomes and increased risk of dyslexia, disturbed verbal execution, and schizophrenia (21).

The frequent occurrence of hypogonadism may have an impact on several diagnoses; it is becoming increasingly evident that low levels of testosterone, apart from its association with osteoporosis, are associated to an unfavorable body composition (abdominal obesity), increased risk of type 2 diabetes, as well as the metabolic syndrome and risk factors of ischemic vascular disease.

The finding of an increased morbidity from infectious diseases has not been described previously. The overall morbidity from all cancers was increased, with more admissions from breast cancer and mediastinal tumors, although the numbers were too small for calculation of CIs. A previous study reported a 50-fold increased risk of male breast cancer among KS subjects (8), although a previous Danish register study did not show an elevated risk (10). The same Danish study found increased incidence of mediastinal tumors.

Diseases of the blood were more frequent among KS subjects, with anemia as the only diagnosis with a significantly increased risk. A decreased hemoglobin concentration is a known consequence of hypogonadism (22).

We found a significantly increased risk of type 1 diabetes, type 2 diabetes, obesity, and hypothyroidism among the KS subjects. Nielsen *et al.* (12) in 1969 found a substantial number of KS subjects with diabetes or glucose intolerance. Swerdlow *et al.* (17) described an elevated mortality from diabetes in KS patients, although we were not able to demonstrate any increased mortality from diabetes in a recent study using the same cohort as the present study (19). Furthermore, low testosterone levels have been shown to predict later type 2 diabetes and the metabolic syndrome in middle-aged men (23), and testosterone treatment increased insulin sensitivity in middle-aged abdominal obese men (24). Type 1 diabetes has not previously been reported with increased frequency in KS, and we cannot rule out misclassification of the diabetes type. However, the same degree of misclassification would be expected in both KS subjects and control subjects; thus, we believe that the finding is clinically relevant. The finding of an increased risk of obesity is consonant with findings from large-scale studies showing an inverse relationship between testosterone level and obesity (25) and is interesting because obesity is a strong predictor of type 2 diabetes.

The risk of hypothyroidism was greatly elevated among KS subjects, although calculation of CIs was not possible due to the small numbers. Previously, an association with congenital hypothyroidism (26) has been suggested, but otherwise only case reports have dealt with an association between hypothyroidism and KS.

The risk of hypogonadism, a hallmark of KS, was greatly elevated as expected, but the diagnosis was only used in 28 of 709 admissions, probably because hypogonadism is considered implicit in a diagnosis of KS and therefore is not necessarily reported as a separate discharge diagnosis.

Because the psychiatric diagnoses changed fundamentally from ICD-8 to ICD-10, a rather crude grouping of diagnoses was made; psychoses, neuroses/disorders of personality, and mental retardation. The risk of all three groups was significantly increased. A previous long-term follow-up study of KS subjects, diagnosed at birth from a chromosome survey, showed an increase of psychiatric referrals among KS subjects compared with control subjects (27). Early studies showed an increased prevalence of KS in penalty institutions and among the mentally retarded, but later follow-up studies among unselected boys from chromosome surveys showed a minor intellectual deficit, mainly a decrease in verbal intelligence (27, 28). KS was associated with more frequent admissions from neurological disorders, with cerebral palsy/paresis and epilepsy as the only diseases with significantly increased frequency. No previous studies, apart from case reports and very small scale studies (29), exist. Our previous study of mortality showed an increased risk of dying from neurological diseases (19).

Our findings of increased morbidity from ischemic heart disease, deep vein thrombosis, pulmonary embolism, and intestinal thrombosis are partly in agreement with previous findings. Previous studies showed increased mortality from circulatory diseases (19), some with increased risk of dying from cerebrovascular events (17, 18) and intestinal thrombosis (17). We were not able to demonstrate any increased risk of cerebrovascular morbidity. In contrast, admissions caused by intestinal thrombosis were very rare (total number only three), although yielding a HR of 7.9 Another study showed an increased risk of deep vein thrombosis and pulmonary embolism (13). The increased risk of ischemic heart disease could in part be explained by low testosterone levels being strongly associated with other risk factors of myocardial infarction (30, 31), diabetes, and the metabolic syndrome (23). We could not confirm the elevated risk of mitral valve prolapse found by Fricke *et al.* (11).

Pneumonia, nonasthmatic chronic obstructive airway disease, and asthma were all more frequent among KS subjects. Increased mortality from pneumonia has been described (17, 19), but no other studies have reported any association between pulmonary diseases and KS. We have no information on smoking habits.

The increased risk of gastrointestinal ulcers and cirrhosis of the liver in KS has not been described. Disturbances of sex hormones are well known in hepatic cirrhosis, but cirrhosis is not a known consequence of hypogonadism.

Eczema and skin infections were more frequent among KS subjects. Associations of any skin disorder are not known in KS, apart from acne as a side effect of testosterone treatment.

As expected, osteoporosis was more frequently diagnosed in KS subjects, probably caused by hypogonadism, but ascertainment bias could also be a part of the explanation, because osteoporosis in KS has frequently been described (5–7). The increased frequency of osteoarthritis has not been described. Previous reports have shown an increased risk of autoimmune/rheumatological disorders (15, 16), especially SLE, but all previous reports are either case reports or small-scale studies with relatively few patients. We were not able to demonstrate a significantly elevated risk of generalized rheumatological diseases in KS. One case of SLE in each group did not allow calculation of a CI.

Urinary tract infections were significantly more frequent among KS subjects, even though hyperplasia of the prostate gland was not. Our previous study of mortality showed an increased risk of dying from urogenital diseases (19). The risk of gynecomastia, traditionally regarded as a hallmark of KS, was greatly elevated (43 times), but only 5% of the KS subjects had that diagnosis, compared with the expected incidence of 50–75% reported by Smyth and Bremner (3) and the 38% reported by Lanfranco *et al.* (14). This may reflect the fact that the true incidence of gynecomastia is lower than previously reported or that gynecomastia is underreported in the National Register of Patients, probably because gynecomastia is considered implicit in the diagnosis of KS (as hypogonadism is).

To our surprise, we found an increased risk of malformations of the heart and urinary tract. No previous studies reported an increased risk of congenital malformations apart from retention of the testes, which previously has been described in as many as 27% of KS subjects, who were referred to an infertility clinic (14). The elevated risk of congenital malformations may in part be explained by the fact that children born with congenital malformations are more prone to have a chromosomal examination performed.

The risk of trauma was significantly increased, with increased risk of osteoporotic fractures (fractures of the spine, hip, and distal forearm). This is the first study to show that the frequently reported osteopenia and osteoporosis in KS subjects, in fact, led to an increased risk of fractures.

Data quality

*Bias.*The overall increased morbidity from nearly all causes may reflect either a truly increased morbidity, ascertainment/surveillance bias, or a combination of both.

Patients with KS may be admitted to hospital more often than non-KS patients, simply because they already suffer from one condition and may therefore encounter more contacts with the health care system. To investigate this potential drawback of this study, we analyzed the risk of admittance in the period before and the period after the diagnosis of KS and found that the elevated risk of admittance was already present before the diagnosis of KS, thus pointing to a minor risk of this kind of bias.

In a previous study of morbidity in Turner syndrome, using the same registers (20), morbidity was elevated for only a minor group of diagnoses and was not generally elevated as in this study. This may indicate that the above-mentioned risk of ascertainment/surveillance bias is not a general problem when using these registers.

Another potential source of bias is the fact that only 25% of the expected number of men with KS are diagnosed (2, 32); thus, the morbidity described in this study can only be applied to the known population of KS subjects. KS subjects who have not been diagnosed may show a profile of morbidity different from what we have described in this report.

The Danish Cytogenetic Central Register represents a unique opportunity for studying chromosomal abnormalities. Virtually all karyotype examinations, abnormal and normal, have been recorded since 1968. The register can be considered complete.

The National Register of Patients has, since 1977, recorded primary and secondary discharge diagnoses for all patients admitted to somatic hospital departments in Denmark. A validation study of the quality of the primary discharge diagnoses showed agreement between two coders and the register data in 73–89% on the three-digit level in the ICD-8 system depending on the clinical subspecialty (33). No validation of the secondary diagnoses or the coding with the ICD-10 system exists. Traditionally, only the primary discharge diagnosis has been used for statistical analysis, mainly because statistics for the background population only include this diagnosis. By including an age-matched control group, we were able to include both primary and secondary diagnoses, because we had the same information in the KS group and the control group.

During the period of investigation, the coding system changed from ICD-8 to ICD-10, and we grouped the two systems into one. We used the same classification system for both groups, and any classification errors will only dilute the observed contrasts.

It is important to stress that all information about the subjects are register data. We have no clinical data, apart from the discharge diagnoses, and no information about relevant exposures, *e.g.* smoking, alcohol consumption, or any information about medical treatment, *e.g.* testosterone treatment.

Conclusions

In this report we describe, for the first time, systematically the morbidity in KS, based on nationwide registers. KS was associated with an increased risk of being admitted to the hospital with virtually any diagnosis. The causes of this increased risk cannot be elucidated in this study, but some of the diagnoses may be caused by the chromosome aberration itself (*e.g.* congenital malformations) or may be linked to hypogonadism (*e.g.* diabetes, obesity, anemia, osteoporosis, and osteoporotic fractures), whereas other diagnoses may be seen as an expression of poor general health, possibly in combination with the poor socioeconomic living conditions that affect many men with KS. Many of the diagnoses represent preventable diseases, and the study points toward increasing the care of patients with KS. Increased awareness of the diagnosis among physicians and better education of patients could lead to better care of KS patients.

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