Footnote 9 14 15 18 20

OXFORD ACADEMIC

JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

ENDOCRINE SOCIETY

Article Navigation

Mortality in Patients with Klinefelter Syndrome in Britain: A Cohort Study

Anthony J. Swerdlow ✉, Craig D. Higgins, Minouk J. Schoemaker, Alan F. Wright, Patricia A. Jacobs

The Journal of Clinical Endocrinology & Metabolism, Volume 90, Issue 12, 1 December 2005, Pages 6516–6522, https://doi.org/10.1210/jc.2005-1077

Published: 01 December 2005 **Article history ▾**

Context: Klinefelter syndrome is characterized by hypogonadism and infertility, consequent on the presence of extra X chromosome(s). There is limited information about long-term mortality in this syndrome because there have been no large cohort studies.

Objective: Our objective was to investigate mortality in men with Klinefelter syndrome.

Design and Setting: We obtained data about patients diagnosed with Klinefelter syndrome at almost all cytogenetics centers in Britain, as far back as records were available, and conducted a cohort study of their mortality, overall and by karyotype.

Patients: We assessed 3518 patients diagnosed since 1959, followed to mid-2003.

Outcome Measure: The outcome measure was standardized mortality ratio (SMR).

Results: A total of 461 deaths occurred. There was significantly raised mortality overall [SMR, 1.5; 95% confidence interval (CI), 1.4–1.7] and from most major causes of death including cardiovascular disease (SMR, 1.3; 95% CI, 1.1–1.5), nervous system disease (SMR, 2.8; 95% CI, 1.6–4.6), and respiratory disease (SMR, 2.3; 95% CI, 1.8–2.9). Mortality was particularly raised from diabetes (SMR, 5.8; 95% CI, 3.4–9.3), epilepsy (SMR, 7.2; 95% CI, 3.1–14.1), pulmonary embolism (SMR, 5.7; 95% CI, 2.5–11.3), peripheral vascular disease (SMR, 7.9; 95% CI, 2.9–17.2), vascular insufficiency of the intestine (SMR, 12.3; 95% CI, 4.0–28.8), renal disease (SMR, 5.0; 95% CI, 2.0–10.3), and femoral fracture (SMR, 39.4; 95% CI, 4.8–142.3). Mortality from ischemic heart disease was significantly decreased (SMR, 0.7; 95% CI, 0.5–0.9).

Conclusions: Patients diagnosed with Klinefelter syndrome have raised mortality from several specific causes. This may reflect hormonal and genetic mechanisms.

Issue Section: Endocrine Care

KLINEFELTER SYNDROME IS a numerical chromosome abnormality in males, characterized by the presence of one or more extra X chromosomes. It occurs in about 1.5 per 1000 of the male population (1). The clinical syndrome was initially described in 1942 (2), and the chromosome constitution was discovered in 1959 (3). Characteristically, the patients have hypogonadism and elevated gonadotropin levels, and various other hormonal and physical abnormalities occur. There has been limited information about long-term mortality risks, however, because of the lack of large cohort (follow-up) studies. The only such published studies have been a cohort of 466 men from a Scottish register (4), later extended to two other centers with a total of 695 men (5), and a cohort of 781 men from Denmark (6). To enable more detailed analyses, based on much larger numbers, we assembled a cohort of cases of Klinefelter syndrome diagnosed in Britain for as long as records are held by the cytogenetics centers in the country and followed up the cohort for mortality, for periods of up to 40 yr. We have previously reported on cancer risks in this cohort (7).

Patients and Methods

We extracted identification and diagnostic data about all patients with Klinefelter syndrome diagnosed as far back as records had been retained (1959 at earliest), from each cytogenetics laboratory in Britain except two small ones. Appropriate ethics committee agreement was obtained for this. Data for the comparatively rare 46,XX male variant of Klinefelter

syndrome were not included in the study because these data have particular potential to include recording and transcription errors from normal males and females. Patients who were recorded as being karyotyped because of cancer were excluded from the study. Identification data about the cohort members were sent to the National Health Service Central Registers (NHSCRs) for England and Wales and for Scotland, which hold records of all NHS patients in their countries and are therefore virtually complete population registers. The registers hold data on deaths, emigrations, and other exits, and therefore the cohort members were flagged on these registers to obtain information on mortality and other losses to follow-up. We were sent death certificates for those who had died. These were coded to the underlying cause of death, using the International Classification of Diseases (ICD) revision employed in Britain at the time of death: ICD7 from 1958–1967, ICD8 from 1968–1978, ICD9 from 1979–1999 in Scotland and 1979–2000 in England and Wales, and ICD10 from 2000 in Scotland and from 2001 in England and Wales. The coding was largely undertaken by the national death coding office, and for the remainder by the authors following the national coding procedures. We then bridge-coded between ICD revisions to give the ICD9 categories shown in the tables. We made an exception for deaths coded under ICD rules to Klinefelter syndrome, which we recoded to the underlying cause that would have applied if Klinefelter had not been written on the certificate; this was done because the purpose of the study was to compare causes of death in Klinefelter patients with the general population, rather than to discover how often certifiers believed Klinefelter to be the cause of other fatal diseases.

For each man in the cohort, we computed person-years of follow-up by 5-yr age group, calendar year, and country (England and Wales *vs.* Scotland), beginning from the date of cytogenetic diagnosis and ending at June 30, 2003, or the 85th birthday, date of death, or other loss to follow-up, whichever was earliest. Follow-up was censored at age 85 because at older ages than this, national (*i.e.* expected) mortality rates are not available by 5-yr age group, and the certified cause of death is often inaccurate. We calculated expected cause-specific mortality in the cohort by multiplying the age-, calendar year-, and country-specific person-years at risk in the cohort by the corresponding national mortality rates for men. Standardized mortality ratios (SMRs) were then calculated as the ratio of observed to expected deaths, and 95% confidence intervals (CIs) for the SMRs were calculated assuming a Poisson distribution (8). Tests for trend and for the difference between SMRs were conducted as described by Breslow and Day (8). Significance tests were two-sided. Absolute excess risks were calculated by subtracting the expected from the observed numbers of deaths and dividing by person-years at risk.

We subdivided the subjects for analysis by the number of sex chromosomes, whether mosaicism was present, and if so, the constitution of the non-Klinefelter component. Where

information was available for mosaics on the numbers of cells diagnosed with each mosaic component, we designated the subject as mosaic only if more than one cell had been counted with each component. We did not have direct information for the study subjects on whether mosaicism was congenital or acquired, but as a rough proxy for this [because the prevalence of acquired mosaicism rises with age (9)], we conducted separate analyses for mosaics diagnosed before age 45 yr and those diagnosed at older ages.

To assess, as far as possible, whether bias might account for certain of the results, we conducted several subanalyses of risks in subdivisions by birth year, risks omitting follow-up and deaths in the early years after cytogenetic diagnosis, and risks omitting cohort members recorded by the Medical Research Council Human Genetics Unit (MRC HGU).

Results

There were 4806 patients with Klinefelter syndrome in the records of the 25 laboratories in the study. The cases had been diagnosed during 1959–2002. At most laboratories, the earliest cases were from the 1960s or early 1970s, depending on when the laboratory was founded and for how long their records had been kept. A total of 1288 cases were not included in the cohort because there was insufficient information for flagging (1224, largely missing date of birth), the year of cytogenetic testing was unknown (24), cytogenetic testing was a consequence of cancer diagnosis (16), cytogenetic testing was conducted after age 85 (two cases), or other reasons (22). The remaining 3518 men were flagged at the NHSCRs and formed the study cohort. The karyotype of most of these men was 47,XXY (3002) or 47,XXY mosaic (320), but 146 had four sex chromosomes, 49 had five sex chromosomes, and one was reported only as Klinefelter syndrome (Table 1). Twenty-two percent had been diagnosed at ages under 15 yr, 62% at 15–44 yr, and 17% at older ages.

TABLE 1.

Cohort by karyotype, age and year of diagnosis, and year of birth

Characteristic	No.	%
Karyotype		
47,XXY	3002	85.3
47,XXY/46,XY	226	6.4
47,XXY/46,XX	22	0.6

Characteristic	No.	%
47,XXY/other mosaic	72	2.1
48,XXXY	55	1.6
48,XXYY	80	2.3
49,XXXXY	48	1.4
48 or 49 sex chromosomes mosaic	12	0.3
Klinefelter unspecified	1	0.03
Age at diagnosis (yr)		
<15	757	21.5
15–24	793	22.5
25–44	1378	39.2
45–64	479	13.6
≥65	111	3.2
Year of diagnosis		
<1970	347	9.9
1970–79	544	15.5
1980–89	952	27.1
≥1990	1675	47.6
Year of birth		
<1930	358	10.2
1930–49	749	21.3
1950–69	1446	41.1
1970–79	450	12.8
≥1980	515	14.6
Total	3518	100.0

View Large

During follow-up of the cohort, 461 subjects died, 17 emigrated, 52 were lost to follow-up in other ways, and 2988 were followed to age 85 or the end of the study period. There were two deaths ascribed by certifiers to Klinefelter syndrome, which we recoded as described in *Patients and Methods*, one to cor pulmonale and one to renal failure. The cohort was followed for 52,987 person-years in total, an average of 15.1 yr per subject.

The all-cause SMR was 1.5 (95% CI, 1.4–1.7), and there was significantly raised mortality from endocrine and metabolic disease, mental disorders, and diseases of the nervous, circulatory, respiratory, and genitourinary systems as well as from congenital anomalies (Table 2). Within more specific categories there were particularly raised risks of death from diabetes (SMR, 5.8; 95% CI, 3.4–9.3), epilepsy (SMR, 7.2; 95% CI, 3.1–14.1), pulmonary embolism (SMR, 5.7; 95% CI, 2.5–11.3), peripheral vascular disease (SMR, 7.9; 95% CI, 2.9–17.2), vascular insufficiency of the intestine (SMR, 12.3; 95% CI, 4.0–28.8), and cardiovascular congenital anomalies (SMR, 7.3; 95% CI, 2.4–17.1). There was also greatly raised mortality from fractures of the femur (SMR, 39.4; 95% CI, 4.8–142.3), but based on only two deaths. Mortality was significantly raised from cerebrovascular disease (SMR, 2.2; 95% CI, 1.6–3.0) but significantly diminished from ischemic heart disease (SMR, 0.7; 95% CI, 0.5–0.9). When the risk of ischemic heart disease was reanalyzed with female rates as expected (not in the table), the SMR was 1.9 (95% CI, 1.4–2.4). The five deaths coded to the ICD rubric vascular insufficiency of the intestine comprised three whose death certificates stated (superior) mesenteric artery thrombosis, and two stated as small bowel infarction or ischemia. Most of the death certificates coded to cerebrovascular disease did not specify whether the cause was thrombotic or hemorrhagic; of those that stated this, there were six deaths due to subarachnoid hemorrhage, four others due to intracerebral hemorrhage, and nine due to cerebrovascular occlusion or thrombosis. Only five of the 17 death certificates for deaths from diabetes stated the diabetes type; four were type 2, and one was type 1. None of the death certificates for the epilepsy deaths indicated any cause of the epilepsy. The mental disorder deaths were mainly due to drug or alcohol abuse/dependence (seven) or dementia (four). All but two of the nine genitourinary system deaths were from renal causes (SMR, 5.0; 95% CI, 2.0–10.3), mainly stated simply as renal failure. We did not analyze cancer deaths by site of the cancer because we have reported this previously (7): in brief, significantly increased risks of mortality from lung and breast cancers and of non-Hodgkin's lymphoma and significantly reduced risk of prostate cancer mortality were found (7).

TABLE 2.

Cause-specific mortality in patients with Klinefelter syndrome overall

ICD9 code	Cause	No. of deaths	SMR (95% CI)	AER per 100,000 per annum
140–208	All malignant neoplasms	99	1.2 (1.0–1.4)	27.7
240–279	Endocrine, metabolic, and nutritional	20	4.8 (2.9–7.4) [a]	29.9
250	Diabetes mellitus	17	5.8 (3.4–9.3) [a]	26.6
290–319	Mental disorders	14	3.7 (2.0–6.2) [a]	19.3
320–389	Diseases of the nervous system	15	2.8 (1.6–4.6) [b]	18.1
345	Epilepsy	8	7.2 (3.1–14.1)[a]	13.0
390–459	Diseases of the circulatory system	163	1.3 (1.1–1.5) [b]	70.4
410–414	Ischemic heart disease	60	0.7 (0.5–0.9) [b]	−48.7
415.1	Pulmonary embolism	8	5.7 (2.5–11.3)[a]	12.5
420–429	Other heart disease	16	2.2 (1.3–3.6) [b]	16.7
424.1	Aortic valve disease	2	2.0 (0.2–7.2)	1.9
430–437	Cerebrovascular disease	46	2.2 (1.6–3.0) [a]	48.0
430	Subarachnoid hemorrhage	6	3.1 (1.2–6.8)[c]	7.7
443.9	Peripheral vascular disease, unspecified	6	7.9 (2.9–17.2)[a]	9.9
460–519	Diseases of the respiratory system	65	2.3 (1.8–2.9) [a]	68.7
480–486	Pneumonia	25	2.3 (1.5–3.4) [a]	26.9

ICD9 code	Cause	No. of deaths	SMR (95% CI)	AER per 100,000 per annum
490–494, 496	Chronic lower respiratory disease	31	2.1 (1.4–3.0)[a]	31.0
520–579	Diseases of the digestive system	19	1.6 (1.0–2.6)	14.0
557	Vascular insufficiency of the intestine	5	12.3 (4.0–28.8)[a]	8.7
580–629	Diseases of the genitourinary system	9	3.6 (1.6–6.8)[b]	12.3
580–593	Renal and ureteric disease	7	5.0 (2.0–10.3)[b]	10.6
740–759	Congenital anomalies	9	6.8 (3.1–13.0)[a]	14.5
745–747	Cardiovascular congenital anomalies	5	7.3 (2.4–17.1)[b]	8.2
800–999	Accidents and violence	32	1.3 (0.9–1.8)	12.8
800–829	Fracture of bones	3	0.4 (0.1–1.3)	−7.2
820–821	Fracture of femur	2	39.4 (4.8–142.3)[b]	3.7
000–999	All causes	461[d]	1.5 (1.4–1.7)[a]	303.4

AER, Absolute excess risk.

[a] $P < 0.001$.

[b] $P < 0.01$.

[c] $P < 0.05$.

[d] Including, as well as the above, 14 deaths from various other specified causes and two from ill-defined causes.

View Large

There was no consistent trend in all-cause SMR with calendar period of death (not in the table) or with attained age (Table 3). The SMR for diabetes increased significantly with age ($P = 0.03$), whereas the opposite was true significantly for mortality from respiratory system diseases ($P = 0.03$) and nonsignificantly for cancer, epilepsy, subarachnoid hemorrhage, and congenital malformations.

TABLE 3.

Cause-specific mortality in patients with Klinefelter syndrome, by attained age

ICD9 code	Cause	Ages <45 yr		Ages 45–64 yr		Ages ≥65 yr	
		No. of deaths	SMR (95% CI)	No. of deaths	SMR (95% CI)	No. of deaths	SMR (95% CI)
140–208	All malignant neoplasms	9	1.4 (0.6–2.7)	49	1.4 (1.0–1.8)[a]	41	1.0 (0.7–1.3)
250	Diabetes mellitus	0	0 (0–11.1)	4	3.8 (1.0–9.6)[a]	13	8.5 (4.6–14.6)[bc]
290–319	Mental disorders	6	3.9 (1.4–8.4)[a]	2	2.1 (0.3–7.7)	6	4.6 (1.7–10.1)[d]
345	Epilepsy	6	8.3 (3.0–18.0)[b]	2	6.4 (0.8–22.9)	0	0 (0–48.7)
390–459	Diseases of the circulatory system	9	1.2 (0.5–2.2)	49	1.0 (0.7–1.3)	105	1.5 (1.3–1.9)[b]
410–414	Ischemic heart disease	5	1.1 (0.4–2.5)	22	0.6 (0.4–0.9)[d]	33	0.8 (0.5–1.1)
430–437	Cerebrovascular disease	4	3.2 (0.9–8.1)	8	1.3 (0.6–2.6)	34	2.6 (1.8–3.6)[b]
430	Subarachnoid hemorrhage	3	4.6 (1.0–13.5)	3	3.2 (0.7–9.3)	0	0 (0–11.7)
460–519	Diseases of the respiratory system	7	3.6 (1.4–7.4)[d]	23	3.0 (1.9–4.5)[b]	35	1.8 (1.3–2.6)[de]
	Pneumonia	4		7		14	

ICD9 code	Cause	Ages <45 yr		Ages 45 –64 yr		Ages ≥65 yr	
		No. of deaths	SMR (95% CI)	No. of deaths	SMR (95% CI)	No. of deaths	SMR (95% CI)
480 –486			3.8 (1.0 –9.7)[a]		2.7 (1.1 –5.6)[a]		2.0 (1.1 –3.3)[a]
490 –494, 496	Chronic lower respiratory disease	1	2.0 (0.1 –11.4)	11	2.6 (1.3 –4.7)[d]	19	1.9 (1.2 –3.0)[a]
520 –579	Diseases of the digestive system	2	1.0 (0.1 –3.6)	4	0.7 (0.2 –1.9)	13	3.1 (1.7 –5.4)[b]
557	Vascular insufficiency of the intestine	0	0 (0 –161.6)	2	12.8 (1.5 –46.1)[a]	3	13.3 (2.7 –38.9)[d]
580 –629	Diseases of the genitourinary system	1	3.7 (0.1 –20.5)	3	4.6 (0.9 –13.4)	5	3.2 (1.0 –7.4)[a]
740 –759	Congenital anomalies	8	8.3 (3.6 –16.3)[b]	1	3.9 (0.1 –21.5)	0	0 (0 –39.2)
800 –999	Accidents and violence	22	1.3 (0.8 –2.0)	8	1.2 (0.5 –2.4)	2	0.9 (0.1 –3.3)
000 –999	All causes	77	1.8 (1.4 –2.2)[b]	153	1.4 (1.2 –1.6)[b]	231	1.6 (1.4 –1.8)[d]

[a] $P < 0.05$.

[b] $P < 0.001$.

[c] SMR increases significantly ($P = 0.03$) with age.

[d] $P < 0.01$.

[e] SMR decreases significantly ($P = 0.03$) with age.

View Large

All-cause mortality was significantly greater for men with mosaic 47,XXY ($P = 0.03$) and nonsignificantly greater for men with more than three sex chromosomes ($P = 0.12$) than in

those with nonmosaic 47,XXY (Table 4). The greater mortality in mosaic than nonmosaic 47,XXY was present to some extent for all major causes of death except circulatory system diseases. There were too few deaths in men with more than three sex chromosomes to assess cause-specific mortality in detail, but there were particularly pronounced risks of mortality from respiratory disease and from congenital anomalies. All deaths from vascular insufficiency of the intestine were in men with a 47,XXY constitution. Ischemic heart disease mortality was significantly diminished in both mosaic and nonmosaic 47,XXY but not, based on small numbers, in men with more than three sex chromosomes.

TABLE 4.

Cause-specific mortality by karyotype

ICD9 code	Cause	47,XXY		47,XXY mosaic		>3 sex chromosomes	
		No. of deaths	SMR (95% CI)	No. of deaths	SMR (95% CI)	No. of deaths	SMR (95% CI)
140–208	All malignant neoplasms	76	1.1 (0.9–1.4)	22	1.7 (1.1–2.5)[a]	2	0.6 (0.1–2.3)
250	Diabetes mellitus	14	6.0 (3.3–10.0)[b]	3	6.5 (1.3–19.0)[a]	0	0 (0–32.7)
290–319	Mental disorders	10	3.1 (1.5–5.8)[c]	4	9.1 (2.5–23.2)[c]	0	0 (0–23.1)
345	Epilepsy	6	6.2 (2.3–13.4)[c]	1	11.4 (0.3–63.4)	1	17.9 (0.5–99.9)
390–459	Diseases of the circulatory system	130	1.3 (1.1–1.5)[c]	24	1.1 (0.7–1.7)	9	2.0 (0.9–3.8)
410–414	Ischemic heart disease	50	0.7 (0.5–1.0)[a]	6	0.4 (0.2–0.9)[a]	4	1.3 (0.3–3.3)
		32		11		3	

ICD9 code	Cause	47,XXY		47,XXY mosaic		>3 sex chromosomes	
		No. of deaths	SMR (95% CI)	No. of deaths	SMR (95% CI)	No. of deaths	SMR (95% CI)
430–437	Cerebrovascular disease		2.0 (1.4–2.8)[b]		2.9 (1.5–5.2)[c]		4.3 (0.9–12.7)
430	Subarachnoid hemorrhage	5	3.1 (1.0–7.2)[a]	1	4.9 (0.1–27.3)	0	0 (0–42.3)
460–519	Diseases of the respiratory system	43	1.9 (1.4–2.6)[b]	17	3.2 (1.9–5.1)[b]	5	5.0 (1.6–11.6)[c]
480–486	Pneumonia	15	1.8 (1.0–3.0)[a]	8	4.0 (1.7–7.8)[c]	2	5.4 (0.7–19.4)
490–494, 496	Chronic lower respiratory disease	20	1.8 (1.1–2.7)[a]	8	2.9 (1.2–5.7)[a]	3	5.8 (1.2–17.1)[a]
520–579	Diseases of the digestive system	13	1.3 (0.7–2.3)	6	4.0 (1.5–8.7)[c]	0	0 (0–8.4)
557	Vascular insufficiency of the intestine	5	15.4 (5.0–35.8)[b]	0	0 (0–56.3)	0	0 (0–264.3)
580–629	Diseases of the genitourinary system	7	3.6 (1.4–7.4)[c]	2	4.4 (0.5–15.9)	0	0 (0–41.1)
740–759	Congenital anomalies	4	3.7 (1.0–9.6)[a]	1	6.7 (0.2–37.6)	4	40.9 (11.1–104.8)[b]
800–999	Accidents and violence	26	1.2 (0.8–1.7)	4	1.9 (0.5–4.8)	2	1.5 (0.2–5.4)
	All causes	349		88		24	

ICD9 code	Cause	47,XXY		47,XXY mosaic		>3 sex chromosomes	
		No. of deaths	SMR (95% CI)	No. of deaths	SMR (95% CI)	No. of deaths	SMR (95% CI)
000–999			1.4 (1.3–1.6)[b]		1.9 (1.5–2.3)[bd]		2.1 (1.3–3.1)[c]

[a] $P < 0.05$.

[b] $P < 0.001$.

[c] $P < 0.01$.

[d] SMR significantly greater ($P = 0.03$) than that for patients with 47,XXY.

View Large

Subdividing mortality in men with mosaic 47,XXY according to the type of mosaic (not in the table), the all-cause SMR was significantly raised for men with a 47,XXY/46,XY constitution (SMR, 1.8; 95% CI, 1.3–2.3) and was slightly greater again for 47,XXY/46,XX (SMR, 2.1; 95% CI, 0.9–4.2) and other mosaic 47,XXY (SMR, 2.1; 95% CI, 1.4–3.0) individuals. There were too few deaths for assessment of cause-specific mortality in these groups. Examining mortality in subjects with mosaic 47,XXY by age at cytogenetic diagnosis, most deaths occurred in patients diagnosed at older ages, but there was no indication that the relative risk of mortality differed by age; the all-cause SMR was 1.9 (95% CI, 1.2–3.0) for patients diagnosed at ages under 45 yr and 1.9 (95% CI, 1.5–2.4) for those diagnosed at older ages.

Subcategory analyses for men with 48, and separately 49, sex chromosomes (not in table) were also limited by small numbers, but the all-cause SMRs for these groups were 1.9 [95% CI, 1.2–3.0 (n = 21)] and 3.5 [95% CI, 0.7–10.4 (n = 3)], respectively.

To check for possible bias caused by selective cytogenetic examination of ill people because of their illness, we reanalyzed the above tables omitting events and person-years in the first year after cytogenetic diagnosis and also omitting the first 3 yr after diagnosis (not in table). With the possible exception of deaths from congenital malformation, the results suggested that there was not appreciable bias; the all-cause SMRs were 1.5 for total follow-up, 1.5 omitting the 1st year of follow-up, and 1.4 omitting the first 3 yr. Major causes of death also showed no appreciable trend except, possibly, congenital malformation mortality, for which SMRs were 6.8 (n = 9), 6.6 (n = 6), and 2.7 (n = 2), respectively.

To examine for potential bias, we also conducted analyses in subcategories by year of birth, because there might be greater potential for selective karyotypic diagnosis in those born many years before karyotyping became widely available, and less potential in those born more recently. The analyses did not suggest any material bias: the all-cause SMR was 1.6 (95% CI, 1.4–1.8) for those born before 1940 and 1.4 (95% CI, 1.1–1.7) for patients born later. To check whether bias had been introduced by inclusion in the cohort of cases from the MRC HGU register, which unlike the other registers was research based rather than clinically based, we reanalyzed excluding the MRC HGU subcohort; the results were not materially affected, with an all-cause SMR of 1.6 (95% CI, 1.4–1.8).

Discussion

The study showed significantly raised mortality from several causes in a cohort large enough to give relatively stable risk estimates. The possibility of bias as an explanation of the results needs careful consideration, however. Inevitably, the study was based on those cases of Klinefelter syndrome that have come to clinical diagnosis; we estimate that this was less than one third of all cases born, even in recent years (7). Cases reaching diagnosis might be phenotypically or in other ways different from those that do not. From a clinical perspective, however, their mortality is that of relevance, because clinical interest is in risks for cases who are recognized as such, not cases who never reach diagnosis. Because this selection might be greater for cases born long before cytogenetic diagnosis was available, we reanalyzed the data excluding cases born before 1940, but there was no material effect on the results.

Second, cytogenetic diagnosis of Klinefelter syndrome might occur as a consequence of clinical diagnosis or care for an illness, mortality from which would then be artifactually raised within the cohort. This effect is obvious for leukemia, for which the diagnostic work-up often includes cytogenetic examination of the bone marrow, and also occurs for other cancers (7). To minimize such effects, we omitted from the analysis individuals known to have been karyotyped because of cancer. It was not practical to detect directly whether there had been similar referrals for nonmalignant diseases, but to examine whether bias had occurred in this way we analyzed risks omitting the early years after cytogenetic diagnosis, when any referral bias would have had its greatest effect; the lack of change in results in these analyses suggests that such bias was negligible, except perhaps for congenital malformation deaths. For the latter cause, some bias is almost inevitable, because by definition congenital conditions must have been present before karyotyping; the number of such deaths was few (2% of all deaths), however, so the bias to overall mortality will not have been material.

We had to omit from the cohort Klinefelter cases whose date of birth was not recorded and cases whose records were no longer retained by the cytogenetic centers. In both instances, bias is not plausible. Date of birth was recorded (or not) at the time of cytogenetic diagnosis, before follow-up and mortality occurred. Destruction of old records was on the basis of year of karyotyping, not on the basis of the particular diagnosis or follow-up.

Confounding seems unlikely to have affected any of the results except possibly those for congenital malformation mortality, because the only known risk factor for Klinefelter syndrome is older maternal age in cases of maternal origin (10), which as far as we know is not associated with any of the noncongenital causes of death examined in the study. Because patients with Klinefelter syndrome (especially those with four or five sex chromosomes) tend to have a low IQ, it is possible that they might have had consequent lifestyles that affected their risks of cause-specific mortality. We do not have relevant information on the behaviors and environments of patients with Klinefelter syndrome to enable assessment of the extent to which this indirect mechanism, rather than a direct effect of chromosomal constitution, could explain the significant findings in our study.

As is usual good practice in epidemiological studies, we censored risk at age 85 yr, because of the diminishing accuracy of death certificate diagnosis with older age (11, 12). The effect of doing otherwise would have been negligible, however, because ages beyond 85 represented only 0.1% of total person-years and 3% of deaths in the cohort. Although death certification at younger ages is also not perfect, this source of information on cause of death was used for both the cohort and the general population comparison, so should not in principle have led to bias.

In the first analyses of mortality in patients with Klinefelter syndrome, Price *et al.* (4) noted excesses of deaths from aortic valve disease (three cases) and subarachnoid hemorrhage (three cases). Price's cohort of 466 patients was from the MRC HGU Register, which is a subset of the present subjects. For aortic valve disease, no additional cases were found in our study beyond those described by Price *et al.* (4), and indeed one of the cases he described was strictly not codable to aortic valve disease as the underlying cause of death. Mortality from this cause is not significantly raised in our much larger cohort, and it appears in retrospect that Price's finding was a chance one. By contrast, three additional deaths from subarachnoid hemorrhage were found in our cohort, and there was a significantly raised risk, suggesting that this cause of death may truly be associated.

The raised risk of cerebrovascular disease mortality is only to a minor extent due to the excess of deaths from subarachnoid hemorrhage. Generalized atheroma seems unlikely to be the explanation for the raised risk, in the light of the significantly reduced SMR for ischemic heart disease. Similarly, the highly significant 12-fold risk of mortality from vascular

insufficiency of the intestine appears to be a specific association with Klinefelter because it is far greater than the general cardiovascular disease risks. No deaths from this cause were seen in the much smaller Danish cohort (6). There was also a significant excess of mortality from peripheral vascular disease and from pulmonary embolism; a raised incidence of pulmonary embolism has been shown previously (13). It seems possible that the various specific cardiovascular mortality excesses are linked, and might all be thromboembolic, reflecting deficient fibrinolysis in Klinefelter syndrome, as a consequence of the androgen deficiency present in the syndrome (14–16). The prevalence of chronic leg ulceration is much raised in Klinefelter (13) and has been shown to be associated with elevated activity of plasminogen activator inhibitor-1, levels of which correlate inversely with testosterone levels (17). Interpretation is complicated, however, because Klinefelter patients are sometimes treated with testosterone, but historically patients sometimes discontinued treatment because it entailed injections; we have no information on the extent of use of testosterone in our cohort.

The significantly diminished risk of ischemic heart disease mortality is unlikely to be due to diminished smoking because the cohort showed raised lung cancer risks (7). It is not what would be expected from the hypoandrogenism in Klinefelter patients. We do not have an explanation for the finding.

A raised prevalence of glucose intolerance has been found in clinical series of Klinefelter patients (18, 19), which appears to be a result of insulin resistance (19). The significantly raised mortality from diabetes in our cohort accords with this, although mortality from this cause was much lower in the smaller Danish cohort (6). We found mortality from diabetes similar in 47,XXY and 47,XXY mosaic patients, although based on small numbers in the latter group. This accords with evidence, although again based on small numbers, that abnormal glucose tolerance is also highly prevalent in both groups (20). No deaths from diabetes occurred in men with more than three sex chromosomes, but the confidence interval was wide.

The raised respiratory mortality in our cohort was seen also in the Danish cohort study (6) and is of uncertain interpretation. Respiratory function testing on a clinical series of patients with Klinefelter syndrome has shown a high prevalence of restrictive defects and of decreased functional residual capacity but not of obstructive disease (21). Pneumonia is a diagnosis that has frequently been entered as the underlying cause of death on death certificates by certifiers in the United Kingdom when it may in fact have been the terminal event in deaths due to another cause (22).

Klinefelter syndrome is associated with decreased bone density (23), and corresponding with this there was a highly significantly raised mortality, albeit based on only two deaths, from

fractured femur, a condition characteristically related to osteoporosis. The excesses of mortality from genitourinary diseases, epilepsy, and substance abuse do not have obvious explanations. The MRC HGU ascertained some patients with Klinefelter syndrome from mental subnormality and penal institutions (24), but exclusion of MRC HGU patients from the cohort did not diminish the SMRs for epilepsy or mental disorders.

Although numbers were too small to analyze cause-specific mortality in patients with four and five sex chromosomes, the progressively greater all-cause SMRs with greater aneuploidy accords with the more severe phenotypic features noted in such patients (25). The greater mortality in mosaic 47,XXY than in nonmosaic 47,XXY patients is not in the direction that would be expected and we have no explanation for it. (It is possible, although unlikely, of course, that despite its statistical significance, it is a chance finding.) The analyses by age at diagnosis did not suggest an association specific to acquired (or to congenital) mosaicism.

Several potential mechanisms might explain raised mortality from specific diseases in patients with Klinefelter syndrome. One is that there is increased expression of X-linked genes before inactivation, or increased dosage of genes on the X chromosome that escape X inactivation (26, 27), that might lead to raised risk. Another is that disease-causing genes in the parents might be associated with risk of nondysjunction as well as risk of disease. An additional possibility is that genes on the X chromosome might predispose to physiological abnormalities (*e.g.* low testosterone concentrations, a high estrogen/testosterone ratio, and sometimes raised estrogen concentrations) (14–16), which could themselves be risk factors for disease. Investigation of the reasons for the raised mortality in Klinefelter syndrome thus has potential to illuminate the broader role of the X chromosome in disease risk in people more generally.

The United Kingdom Clinical Cytogenetics Group comprises the authors of this work plus Paul J. Batstone (Inverness Genetics Laboratory), Leslie J. Butler (NE Thames, Great Ormond Street Hospital Genetics Laboratory), Teresa Davies (Bristol Genetics Laboratory), Valerie Davison (Birmingham Genetics Laboratory), Zoe Docherty (SE Thames, Guy's Hospital Genetics Laboratory), David P. Duckett (Leicestershire Genetics Centre), Margaret Fitchett (Oxford Genetics Laboratory), Alison Fordyce (MRC Human Genetics Unit, Edinburgh), Lorraine Gaunt (Manchester Genetics Laboratory), Elizabeth Grace (Edinburgh Genetics Laboratory), Peter Howard (Liverpool Genetics Laboratory), Gordon W. Lowther (Glasgow Genetics Laboratory), Christine Maliszewska (Dundee Genetics Laboratory), Edna L. Maltby (Sheffield Genetics Laboratory), Kevin P. Ocraft (Nottingham Genetics Laboratory), Selwyn Roberts (Wales Genetics Laboratory), Kim K. Smith (Cambridge Genetics Laboratory), Gordon S. Stephen (Aberdeen Genetics Laboratory), John W. Taylor (SW Thames, St. George's Hospital Genetics Laboratory), Catherine S. Waters (NW Thames, Northwick Park

Hospital Genetics Laboratory), Jeffery Williams (Leeds Genetics Laboratory), John Wolstenholme (Newcastle Genetics Laboratory), and Sheila Youings (Wessex Regional Genetics Laboratory).

We thank D. Allen, F. Barber, C. Maguire, P. Murnaghan, M. Pelerin, and M. Swanwick for assistance in data collection; E. Boyd, D. Couzin, J. Delhanty, P. Ellis, M. Faed, J. Fennell, A. Kessling, A. McDermott, A. Parkin, A. Potter, and D. Ravine for access to data; N. Mudie and A. Hart for help in coding; H. Nguyen for data entry; Z. Qiao for computer programming; N. Dennis and R. Stanhope for advice; the NHSCRs and cancer registries of England, Wales, and Scotland for follow-up data; and Mrs. M. Snigorska for secretarial help.

This work was supported by a grant from the United Kingdom Medical Research Council.

First Published Online October 4, 2005

Abbreviations:

CI, Confidence interval;

ICD, International Classification of Diseases;

SMR, standardized mortality ratio.

References

1 Bojesen A, Juul S, Gravholt CH 2003 Prenatal and postnatal prevalence of Klinefelter syndrome: a national registry study. *J Clin Endocrinol Metab* 88:622–626
Google Scholar Crossref PubMed

2 Klinefelter Jr HG, Reifenstein Jr EC, Albright F 1942 Syndrome characterized by gynecomastia, aspermatogenesis without a-Leydigism and increased excretion of follicle-stimulation hormone. *J Clin Endocrinol Metab* 2:615–627
Google Scholar Crossref

3 Jacobs PA, Strong JA 1959 A case of human intersexuality having a possible XXY sex-determining mechanism. *Nature* 183:302–303
Google Scholar Crossref PubMed

4 Price WH, Clayton JF, Wilson J, Collyer S, de Mey R 1985 Causes of death in X chromatin positive males (Klinefelter's syndrome). *J Epidemiol Community Health* 39:330–336
Google Scholar Crossref PubMed

5 Swerdlow AJ, Hermon C, Jacobs PA, Alberman E, Beral V, Daker M, Fordyce A, Youings S 2001 Mortality and cancer incidence in persons with numerical sex chromosome abnormalities: a cohort study. *Ann Hum Genet* 65:177–188
Google Scholar Crossref PubMed

6 Bojesen A, Juul A, Birkebæk N, Gravholt CH 2004 Increased mortality in Klinefelter syndrome. *J Clin Endocrinol Metab* 89:3330–3834
Google Scholar Crossref

7 Swerdlow AJ, Schoemaker MJ, Higgins C, Wright AF, Jacobs PA; UK Clinical Cytogenetics Group 2005 Cancer incidence and mortality in men with Klinefelter syndrome: a cohort study. *J Natl Cancer Inst* 97:1204–1210
Google Scholar Crossref PubMed

8 Breslow NE, Day NE 1987 Statistical methods in cancer research. Vol II. The design and analysis of cohort studies. IARC Scientific Publication No. 82. Lyon, France: International Agency for Research on Cancer

9 Jacobs PA, Court Brown WM, Doll R 1961 Distribution of human chromosome counts in relation to age. *Nature* 191:1178–1180
Google Scholar Crossref PubMed

10 Thomas NS, Ennis S, Sharp AJ, Durkie M, Hassold TJ, Collins AR, Jacobs PA 2001 Maternal sex chromosome non-disjunction: evidence for X chromosome-specific risk factors. *Hum Mol Genet* 10:243–250
Google Scholar Crossref PubMed

11 Cameron HM, McGoogan E 1981 A prospective study of 1152 hospital autopsies. I. Inaccuracies in death certification. *J Pathol* 133:275–283

12 Swerdlow A, dos Santos Silva I, Doll R 2001 Cancer incidence and mortality in England and Wales: trends and risk factors. Oxford, UK: Oxford University Press

13

Campbell WA, Price WH 1981 Venous thromboembolic disease in Klinefelter's syndrome. *Clin Genet* 19:275–280
Google Scholar Crossref PubMed

14 Wang C, Baker HWG, Burger HG, de Kretser DM, Hudson B 1975 Hormonal studies in Klinefelter's syndrome. *Clin Endocrinol* 4:399–411
Google Scholar Crossref

15 Plymate SR, Leonard JM, Paulsen CA, Fariss BL, Karpas AE 1983 Sex hormone-binding globulin changes with androgen replacement. *J Clin Endocrinol Metab* 57:645–648
Google Scholar Crossref PubMed

16 Grumbach MM, Conte FA 1998 Disorders of sex differentiation. *In: Wilson JD, Foster DW, Kronenberg HM, Larsen PR, eds. Williams textbook of endocrinology. 9th ed. Philadelphia: WB Saunders;* 1303–1425

17 Zollner TM, Veraart JCJM, Wolter M, Hesse S, Villemur B, Wenke A, Werner RJ, Boehncke WH, Jost SS, Scharrer I, Kaufmann R 1997 Leg ulcers in Klinefelter's syndrome: further evidence for an involvement of plasminogen activator inhibitor-1. *Br J Dermatol* 136:341–344
Google Scholar Crossref PubMed

18 Nielsen J 1972 Diabetes mellitus in patients with aneuploid chromosome aberrations and in their parents. *Humangenetik* 16:165–170
Google Scholar Crossref PubMed

19 Geffner ME, Kaplan SA, Bersche N, Lippe BM, Landaw EM, Bergman RN, Golde DW 1987 Insulin resistance in Klinefelter syndrome. *J Pediatr Oncol* 2:173–178

20 Nielsen J, Johansen K, Yde H 1969 Frequency of diabetes mellitus in patients with Klinefelter's syndrome of different chromosome constitutions and the XYY syndrome: plasma insulin and growth hormone level after a glucose load. *J Clin Endocrinol Metab* 29:1062–1073
Google Scholar Crossref PubMed

21 Huseby JS, Petersen D 1981 Pulmonary function in Klinefelter's syndrome. *Chest* 80:31–33
Google Scholar Crossref PubMed

22

Ashley J, Devis T 1992 Death certification from the point of view of the epidemiologist. *Popul Trends* 67:22–28

23 Horowitz M, Wishart JM, O'Loughlin PD, Morris HA, Need AG, Nordin BEC 1992 Osteoporosis and Klinefelter's syndrome. *Clin Endocrinol* 36:113–118
Google Scholar Crossref

24 Court Brown WM 1969 Sex chromosome aneuploidy in man and its frequency, with special reference to mental subnormality and criminal behavior. *Int Rev Exp Pathol* 7:31–97
Google Scholar PubMed

25 Jones KL 1997 Smith's recognizable patterns of human malformation. 5th ed. Philadelphia: WB Saunders

26 Carrel L, Willard HF 1999 Heterogeneous gene expression from the inactive X chromosome: an X-linked gene that escapes X inactivation in some human cell lines but is inactivated in others. *Proc Natl Acad Sci USA* 96:7364–7369
Google Scholar Crossref PubMed

27 Brown CJ, Greally JM 2003 A stain upon the silence: genes escaping X inactivation. *Trends Genet* 19:432–438
Google Scholar Crossref PubMed

View Metrics

More on this topic

Prenatal and Postnatal Prevalence of Klinefelter Syndrome: A National Registry Study

Effects of Oxandrolone on Cardiometabolic Health in Boys With Klinefelter Syndrome: A Randomized Controlled Trial

Mild Deficits of Cortical Bone in Young Adults With Klinefelter Syndrome or Anorchia Treated With Testosterone

Anthropometry in Klinefelter Syndrome - Multifactorial Influences Due to CAG Length, Testosterone Treatment and Possibly Intrauterine Hypogonadism

Related articles in

Web of Science

Google Scholar

Related articles in PubMed

A GWAS identifies gastric cancer susceptibility loci at 12q24.11-12 and 20q11.21.

Genetic variation in a colonization specialist, Simulium ruficorne (Diptera: Simuliidae), the world's most widely distributed black fly.

De novo unbalanced translocations have a complex history/aetiology.

Dysregulated Expression and Subcellular Localization of Base Excision Repair (BER) Pathway Enzymes in Gallbladder Cancer.

Citing articles via

Web of Science (113)

Google Scholar

CrossRef

Latest | **Most Read** | **Most Cited**

Maternal High Triglyceride Levels During Early Pregnancy and Risk of Preterm Delivery: A Retrospective Cohort Study

Adiposity, Insulin Resistance, and Bone Mass in Children and Adolescents

A new multi-system disorder caused by the Gαs mutation p.F376V

Characterization of the CYP11A1 Non-synonymous Variant p.E314K in Children Presenting with Adrenal Insufficiency

Statin treatment decreases mitochondrial respiration but muscle coenzyme Q10 levels are unaltered: The LIFESTAT study

JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Online ISSN 1945-7197

Print ISSN 0021-972X