

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

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## **Abstract**

**Context:** Klinefelter syndrome is characterised 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. **Objectives:** To investigate mortality in men with Klinefelter syndrome. **Design & Setting:** We obtained data about patients diagnosed with Klinefelter syndrome at almost all cytogenetics centres in Britain, as far back as records were available, and conducted a cohort study of their mortality, overall and by karyotype. **Patients:** 3518 patients diagnosed since 1959, followed to mid-2003. **Outcome measure:** Standardised mortality ratio (SMR). **Results:** 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 ischaemic 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.

## **Introduction**

Klinefelter syndrome is a numerical chromosome abnormality in males, characterised by the presence of one or more extra X chromosomes. It occurs in about 1.5 in a thousand 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 centres with a total of 695 men (5), and a cohort of 781 men from Denmark (6). In order 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 centres in the country, and followed the cohort up for mortality, for periods of up to 40 years. We have previously reported on cancer risks in this cohort (7).

## **Materials 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 to 1967, ICD8 from 1968 to 1978, ICD9 from 1979 to 1999 in Scotland and 1979 to 2000 in England & Wales, and ICD10 from 2000 in Scotland and from 2001 in England & 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 re-coded 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 year age-group, calendar year and country (England & Wales vs Scotland), beginning from the date of cytogenetic diagnosis and ending at 30 June 2003 or the 85<sup>th</sup> 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 year 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.

Standardised 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 & Day (8). Significance tests were 2-sided. Absolute excess risks (AERs) 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 only designated the subject as mosaic if more than 1 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 years, and those diagnosed at older ages.

In order 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 risk 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. 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 (2 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 4 sex chromosomes, 49 had 5 sex chromosomes, and 1 was reported only as 'Klinefelter syndrome' (Table 1). 22% had been diagnosed at ages under 15, 62% at 15-44 years, and 17% at older ages.

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 2 deaths ascribed by certifiers to Klinefelter syndrome, which we recoded as described under 'Methods' – one to cor pulmonale and one to renal failure. The cohort were followed for 52,987 person-years in total, an average of 15.1 years 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 2 deaths. Mortality was significantly raised from cerebrovascular disease (SMR, 2.2; 95% CI, 1.6 – 3.0), but significantly diminished from ischaemic heart disease (SMR, 0.7; 95% CI, 0.5 – 0.9). When the risk of ischaemic heart disease was re-analysed with female rates as expected (not in 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 3 whose death certificates stated (superior) mesenteric artery thrombosis, and two stated as small bowel infarction or ischaemia. Most of the death certificates coded to cerebrovascular disease did not specify whether the cause was thrombotic or haemorrhagic; of those that stated this, there were 6 deaths due to subarachnoid haemorrhage, 4 others due to intracerebral haemorrhage, and 9 due to cerebrovascular occlusion or thrombosis. Only 5 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 (7) or dementia (4). 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 analyse 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).

There was no consistent trend in all-cause SMR, with calendar period of death (not in 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 non-significantly for cancer, epilepsy, subarachnoid haemorrhage, and congenital malformations.

All-cause mortality was significantly greater for men with mosaic 47,XXY ( $p = 0.03$ ) and non-significantly greater for men with more than 3 sex chromosomes ( $p = 0.12$ ) than in those with non-mosaic 47,XXY (Table 4). The greater mortality in mosaic than non-mosaic 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 3 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. Ischaemic heart disease mortality was significantly diminished in both mosaic and non-mosaic 47,XXY, but not, based on small numbers, in men with more than 3 sex chromosomes.

Subdividing mortality in men with mosaic 47,XXY according to the type of mosaic (not in 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 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.

In order to check for possible bias caused by selective cytogenetic examination of ill people because of their illness, we reanalysed the above tables omitting events and person-years in the first year after cytogenetic diagnosis, and also omitting the first three years 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 first year of follow-up, and 1.4 omitting the first 3 years. 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 registries was research-based rather than clinically-based, we re-analysed 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 a 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 recognised as such, not cases who never reach diagnosis. Because this selection might be greater for cases born long before cytogenetic diagnosis was available, we reanalysed the data excluding cases born before 1940, but there was no material effect on the results.

Secondly, cytogenetic diagnosis of Klinefelter syndrome might occur as a consequence of clinical diagnosis or care for an illness, mortality from which would then be artefactually raised within the cohort. This effect is obvious for leukaemia, for which the diagnostic work-up often includes cytogenetic examination of the bone marrow, and also occurs for other cancers (7). To minimise such effects we omitted from the analysis individuals known to have been karyotyped because of cancer. It was not practical to detect whether there had been similar referrals for non-malignant diseases, but to examine whether bias had occurred in this way we analysed 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 centres. 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 non-congenital causes of death examined in the study. As patients with Klinefelter syndrome (especially those with 4 or 5 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 behaviours 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 years, 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 (3 cases) and subarachnoid haemorrhage (3 cases). Price's cohort of 466 patients was from the MRC Human Genetics Unit Register, which is a subset of the present subjects. For aortic valve disease no further 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 further deaths from subarachnoid haemorrhage 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 haemorrhage. Generalised atheroma seems unlikely to be the explanation for the raised risk, in the light of the significantly reduced SMR for ischaemic 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 as 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 – 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 ischaemic heart disease (IHD) 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 due to 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 3 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 UK 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 2 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 Human Genetics Unit (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 analyse cause-specific mortality in patients with 4 and 5 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 non-mosaic 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 prior to 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 non-dysjunction as well as risk of disease. A further possibility is that genes on the X chromosome might predispose to physiological abnormalities (e.g. low testosterone concentrations, a high oestrogen/testosterone ratio and sometimes raised oestrogen 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.

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**Table 1 Cohort by karyotype, age and year of diagnosis, and year of birth**

<b>Characteristic</b>	<b>No.</b>	<b>%</b>
<b>Karyotype</b>		
47,XXY	3002	85.3
47,XXY/46,XY	226	6.4
47,XXY/46,XX	22	0.6
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
<b>Age at diagnosis (years)</b>		
<15	757	21.5
15-24	793	22.5
25-44	1378	39.2
45-64	479	13.6
≥65	111	3.2
<b>Year of diagnosis</b>		
<1970	347	9.9
1970-79	544	15.5
1980-89	952	27.1
≥1990	1675	47.6
<b>Year of birth</b>		
<1930	358	10.2
1930-49	749	21.3
1950-69	1446	41.1
1970-79	450	12.8
≥1980	515	14.6
<b>Total</b>	<b>3518</b>	<b>100.0</b>

**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
240-79	Endocrine, metabolic & nutritional	20	4.8 (2.9 – 7.4) <sup>a</sup>	29.9
250	Diabetes mellitus	17	5.8 (3.4 – 9.3) <sup>a</sup>	26.6
290-319	Mental disorders	14	3.7 (2.0 – 6.2) <sup>a</sup>	19.3
320-89	Diseases of the nervous system	15	2.8 (1.6 – 4.6) <sup>b</sup>	18.1
345	Epilepsy	8	7.2 (3.1 – 14.1) <sup>a</sup>	13.0
390-459	Diseases of the circulatory system	163	1.3 (1.1 – 1.5) <sup>b</sup>	70.4
410-4	Ischaemic heart disease	60	0.7 (0.5 – 0.9) <sup>b</sup>	-48.7
415.1	Pulmonary embolism	8	5.7 (2.5 – 11.b) <sup>a</sup>	12.5
420-9	Other heart disease	16	2.2 (1.3 – 3.6) <sup>b</sup>	16.7
424.1	Aortic valve disease	2	2.0 (0.2 – 7.2)	1.9
430-7	Cerebrovascular disease	46	2.2 (1.6 – 3.0) <sup>a</sup>	48.0
430	Subarachnoid haemorrhage	6	3.1 (1.2 – 6.8) <sup>c</sup>	7.7
443.9	Peripheral vascular disease, unspecified	6	7.9 (2.9 – 17.b) <sup>a</sup>	9.9
460-519	Diseases of the respiratory system	65	2.3 (1.8 – 2.9) <sup>a</sup>	68.7
480-6	Pneumonia	25	2.3 (1.5 – 3.4) <sup>a</sup>	26.9
490-4, 496	Chronic lower respiratory disease	31	2.1 (1.4 – 3.0) <sup>a</sup>	31.0
520-79	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) <sup>a</sup>	8.7
580-629	Diseases of the genitourinary system	9	3.6 (1.6 – 6.8) <sup>b</sup>	12.3
580 – 93	Renal and ureteric disease	7	5.0 (2.0 – 10.3) <sup>b</sup>	10.6
740-59	Congenital anomalies	9	6.8 (3.1 – 13.0) <sup>a</sup>	14.5
745 - 47	Cardiovascular congenital anomalies	5	7.3 (2.4 – 17.1) <sup>b</sup>	8.2
800-999	Accidents and violence	32	1.3 (0.9 – 1.8)	12.8
800-29	Fracture of bones	3	0.4 (0.1 – 1.3)	-7.2
820-1	Fracture of femur	2	39.4 (4.8 – 142.3) <sup>b</sup>	3.7
000 - 999	All causes	461 <sup>d</sup>	1.5 (1.4 – 1.7) <sup>a</sup>	303.4

ICD, International classification of diseases; SMR, standardised mortality ratio; AER, absolute excess risk.

<sup>a</sup>p<0.001

<sup>b</sup>p<0.01

<sup>c</sup>p<0.05

<sup>d</sup>Including, as well as the above, 14 deaths from various other specified causes and 2 from ill-defined causes.

**Table 3 Cause-specific mortality in patients with Klinefelter syndrome, by attained age**

ICD9 code	Cause	Ages <45		Ages 45-64		Ages ≥65	
		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) <sup>a</sup>	41	1.0 (0.7 – 1.3)
250	Diabetes mellitus	0	0 (0 – 11.1)	4	3.8 (1.0 – 9.6) <sup>a</sup>	13	8.5 (4.6 – 14.6) <sup>b,c</sup>
290-319	Mental disorders	6	3.9 (1.4 – 8.4) <sup>a</sup>	2	2.1 (0.3 – 7.7)	6	4.6 (1.7 – 10.1) <sup>d</sup>
345	Epilepsy	6	8.3 (3.0 – 18.0) <sup>b</sup>	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) <sup>b</sup>
410-4	Ischaemic heart disease	5	1.1 (0.4 – 2.5)	22	0.6 (0.4 – 0.9) <sup>d</sup>	33	0.8 (0.5 – 1.1)
430-7	Cerebrovascular disease	4	3.2 (0.9 – 8.1)	8	1.3 (0.6 – 2.6)	34	2.6 (1.8 – 3.6) <sup>b</sup>
430	Subarachnoid haemorrhage	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) <sup>d</sup>	23	3.0 (1.9 – 4.5) <sup>b</sup>	35	1.8 (1.3 – 2.6) <sup>d,e</sup>
480-6	Pneumonia	4	3.8 (1.0 – 9.7) <sup>a</sup>	7	2.7 (1.1 – 5.6) <sup>a</sup>	14	2.0 (1.1 – 3.3) <sup>a</sup>
490-4, 496	Chronic lower respiratory disease	1	2.0 (0.1 – 11.4)	11	2.6 (1.3 – 4.7) <sup>d</sup>	19	1.9 (1.2 – 3.0) <sup>a</sup>
520-79	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) <sup>b</sup>
557	Vascular insufficiency of the intestine	0	0 (0 – 161.6)	2	12.8 (1.5 – 46.1) <sup>a</sup>	3	13.3 (2.7 – 38.9) <sup>d</sup>
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) <sup>a</sup>
740-59	Congenital anomalies	8	8.3 (3.6 – 16.3) <sup>b</sup>	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) <sup>b</sup>	153	1.4 (1.2 – 1.6) <sup>b</sup>	231	1.6 (1.4 – 1.8) <sup>d</sup>

ICD, International classification of diseases; SMR, standardised mortality ratio; CI, confidence interval.

<sup>a</sup>p<0.05.

<sup>b</sup>p<0.001.

<sup>c</sup>SMR increases significantly (p = 0.03) with age.

<sup>d</sup>p<0.01

<sup>e</sup>SMR decreases significantly (p= 0.03) with age.

**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) <sup>a</sup>	2	0.6 (0.1 – 2.3)
250	Diabetes mellitus	14	6.0 (3.3 – 10.0) <sup>b</sup>	3	6.5 (1.3 – 19.0) <sup>a</sup>	0	0 (0 – 32.7)
290-319	Mental disorders	10	3.1 (1.5 – 5.8) <sup>c</sup>	4	9.1 (2.5 – 23.2) <sup>c</sup>	0	0 (0 – 23.1)
345	Epilepsy	6	6.2 (2.3 – 13.4) <sup>c</sup>	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) <sup>c</sup>	24	1.1 (0.7 – 1.7)	9	2.0 (0.9 – 3.8)
410-4	Ischaemic heart disease	50	0.7 (0.5 – 1.0) <sup>a</sup>	6	0.4 (0.2 – 0.9) <sup>a</sup>	4	1.3 (0.3 – 3.3)
430-7	Cerebrovascular disease	32	2.0 (1.4 – 2.8) <sup>b</sup>	11	2.9 (1.5 – 5.2) <sup>c</sup>	3	4.3 (0.9 – 12.7)
430	Subarachnoid haemorrhage	5	3.1 (1.0 – 7.2) <sup>a</sup>	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) <sup>b</sup>	17	3.2 (1.9 – 5.1) <sup>b</sup>	5	5.0 (1.6 – 11.6) <sup>c</sup>
480-6	Pneumonia	15	1.8 (1.0 – 3.0) <sup>a</sup>	8	4.0 (1.7 – 7.8) <sup>c</sup>	2	5.4 (0.7 – 19.4)
490-4, 496	Chronic lower respiratory disease	20	1.8 (1.1 – 2.7) <sup>a</sup>	8	2.9 (1.2 – 5.7) <sup>a</sup>	3	5.8 (1.2 – 17.1) <sup>a</sup>
520-79	Diseases of the digestive system	13	1.3 (0.7 – 2.3)	6	4.0 (1.5 – 8.7) <sup>c</sup>	0	0 (0 – 8.4)
557	Vascular insufficiency of the intestine	5	15.4 (5.0 – 35.8) <sup>b</sup>	0	0 (0 – 56.3)	0	0 (0 – 264.3)
580-629	Diseases of the genitourinary system	7	3.6 (1.4 – 7.4) <sup>c</sup>	2	4.4 (0.5 – 15.9)	0	0 (0 – 41.1)
740-59	Congenital anomalies	4	3.7 (1.0 – 9.6) <sup>a</sup>	1	6.7 (0.2 – 37.6)	4	40.9 (11.1 – 104.8) <sup>b</sup>
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)
000 – 999	All causes	349	1.4 (1.3 – 1.6) <sup>b</sup>	88	1.9 (1.5 – 2.3) <sup>b,d</sup>	24	2.1 (1.3 – 3.1) <sup>c</sup>

ICD, International classification of diseases; SMR, standardised mortality ratio; CI, confidence interval.

<sup>a</sup>p<0.05.

<sup>b</sup>p<0.001.

<sup>c</sup>p<0.01.

<sup>d</sup>SMR significantly greater (p = 0.03) than that for patients with 47,XXY

