

Increased Mortality in Klinefelter Syndrome

ANDERS BOJESEN, SVEND JUUL, NIELS BIRKEBÆK, AND CLAUS H. GRAVHOLT

Medical Department M. (Diabetes and Endocrinology), Aarhus Sygehus, Aarhus University Hospital (A.B., C.H.G.); Department of Epidemiology and Social Medicine, Aarhus University (S.J.); and Department of Pediatrics, Skejby Hospital, Aarhus University Hospital (N.B.), DK-8000 Aarhus C, Denmark

Klinefelter syndrome (KS) is the most prevalent sex chromosome disorder in man and is a common cause of hypogonadism. To describe mortality in KS, we conducted an epidemiological study, using Danish registers covering the entire nation. We constructed a cohort of 781 Danish boys and men diagnosed with KS (from the Danish Cytogenetic Central Register) and a control group of 3803 men, matched by month and year of birth. Vital status was obtained from the Centralized Civil Register, and causes of death were obtained from the National Register of Causes of Death. We used Cox regression with stratification on groups of diagnoses according to International Classification of Diseases, 10th version. Where sig-

nificant results were found, subsequent analyses were performed on subdivisions of diagnoses. We found that Klinefelter syndrome was associated with a significant increase in mortality risk of 40% (hazard ratio, 1.40; 95% confidence interval, 1.13–1.74), corresponding to a significantly reduced median survival of 2.1 yr. The increased mortality was mainly due to increased mortality from infectious, neurological, circulatory, pulmonary, and urinary tract diseases. Whether this increase is caused by the syndrome *per se* (i.e. hypogonadism) or other factors, e.g. socioeconomic, are involved is presently unknown. (*J Clin Endocrinol Metab* 89: 3830–3834, 2004)

KLINEFELTER SYNDROME (KS) is the most common sex chromosome disorder, affecting one in every 600 males (1, 2). Affected males carry an additional X chromosome (or more), which results in maldevelopment of the testis, leading to hypogonadism and infertility. Other important findings in KS are learning difficulties, eunuchoid appearance, gynecomastia, increased height, small testes (<4 ml), and elevated gonadotropin levels (3). Only approximately 25% of the expected number of men with KS are diagnosed, and most of these are diagnosed in adulthood (2, 4).

The mortality and causes of death in KS patients are largely unknown; only two epidemiologic studies have been conducted. Swerdlow *et al.* (5) reported a significantly increased mortality from all causes (relative risk, 1.63), with 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. Price *et al.* (6) reported a significantly overall increased mortality (relative risk, 1.50), with increased risk of dying from circulatory and cerebrovascular diseases. Both studies only examined the primary cause of death. Case reports and cross-sectional studies have shown an increased prevalence of diabetes mellitus (7), osteoporosis (8–11), mitral valve prolapse (12), and autoimmune diseases, particularly systemic lupus erythematosus (13, 14).

To describe mortality in men suffering from KS in more detail, we used Danish registers covering the entire nation.

Abbreviations: CI, Confidence interval; ICD-8, International Classification of Diseases, eighth version; KS, Klinefelter syndrome.

JCEM is published monthly by The Endocrine Society (<http://www.endo-society.org>), the foremost professional society serving the endocrine community.

Materials and Methods

The registers

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 (www.cpr.dk). The personal identification number is used for a number of administrative purposes and is included in a number of registers, thus providing a unique opportunity for record linkage.

The Danish Cytogenetic Central Register has been recording all cytogenetic examinations performed in Denmark, both prenatal and postnatal, since 1960. In Denmark, seven laboratories perform postnatal karyotyping, and five of these also perform prenatal karyotyping. The register includes information on karyotype, date of diagnosis, maternal age, whether pre- or postnatal [and if prenatal, the methodology used (amniocentesis or chorion villus sampling)], and the outcome of the pregnancy (induced abortion, spontaneous abortion, or live born). The register 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 has no information regarding phenotype. The reasons for performing karyotype examinations have been described previously (15).

The Danish Register of Causes of Death contains computerized death certificate information for all deaths in Denmark since 1973, including date of death, up to four causes of death [International Classification of Diseases, eighth version (ICD-8) and ICD-10 diagnoses], and manner of death (five possible manners: natural, accident, suicide, homicide, and unexplained (no information available) (16). The most recent update covers the period 1973–1999.

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

The cohort

We created a cohort based on all males diagnosed with KS (859 men) from the Danish Cytogenetic Central Register. Seventy-one of these were not included because they either died before January 1, 1973, or were diagnosed after December 31, 1999. We also excluded three subjects who were diagnosed postmortem and four subjects who died in their first year of life; they all had coexisting trisomy 18, which usually is a lethal chromosome disorder. An age- and calendar time-matched control cohort was created from the Danish Civil Register by extracting five ran-

domly selected men, matched by month and year of birth, for each KS subject (3,905 men). Information on civil status (alive, dead, emigrated, or disappeared) was also extracted for both KS and control subjects. We excluded 102 control subjects who died before the diagnosis of KS in their corresponding KS subject. The final cohort consisted of 781 KS subjects (11,917 person-years) and 3,803 control subjects (60,722 person-years).

Information on vital status (alive, dead, emigrated, or disappeared) was extracted for both KS and control subjects. Time at risk started at the date of KS diagnosis or January 1, 1973, whichever came last, for both the KS subjects and their matching controls. Censoring of individuals took place on December 31, 1999, or at the time of emigration or disappearance, whichever came first.

Information on causes of death was obtained from the Danish Register of Causes of Death.

Statistical analysis

Hazard ratios were calculated using Cox regression analysis with stratification, using each KS patient and his matched controls as a stratum. Kaplan-Meier survival estimates were constructed from age at entry in and age at exit from the cohort. The matching ensured that comparisons were adjusted for age and calendar time. Cause-specific mortality hazard ratios were first calculated for each of 16 ICD-10 chapters; ICD-8 codes were translated to the same classification. If a significant hazard ratio was found in a chapter, we also analyzed chapter subgroups. Hazard ratios for specific diagnoses of interest, based on previous reports (5, 6), were also calculated. To estimate cause-specific hazard ratios, deaths from other causes were censored. In some chapters, statistical analysis was impossible because of too few deaths.

The matching gave us a unique opportunity to study not only the primary cause of death, but all recorded contributing causes of death (up to four contributing causes can be recorded in a death certificate). We analyzed both the primary cause of death and any contributing cause of death. When analyzing all contributing causes, only one diagnosis from a chapter was counting if it occurred more than once. As an example, if a subject had cardiac insufficiency as primary death diagnosis and myocardial infarction as secondary death diagnosis, only one chapter 7 diagnosis was included.

$P < 0.05$ was considered significant. All results are shown with 95% confidence intervals (CIs). We made no formal corrections for multiple comparisons. Intercooled Stata 8.1 for Windows (Stata Corp., College Station, TX) was used for all calculations.

Results

Mortality from all causes

The mortality among KS men was 40% higher than that among population controls (hazard ratio, 1.40; 95% CI, 1.13–1.74; $P = 0.002$). The median survival age among KS subjects was 71.4 yr compared with 73.5 yr in controls, a difference of 2.1 yr (95% CI, 0.3–3.9; Fig. 1). Apart from the KS subjects with coexisting trisomy 18, one death occurred during the perinatal period due to renal agenesis (Potter syndrome) in a KS subject.

Cause-specific mortality

During the follow-up period (January 1, 1973, to December 31, 1999), 124 KS subjects and 491 control subjects died and were registered in the Danish Register of Causes of Death. Hazard ratios for all chapters are shown in Table 1.

Primary cause of death. At the chapter level we found a significantly increased mortality among KS subjects from infectious diseases, pulmonary diseases, and urinary tract diseases. We found no additional statistically significant increased mortality risk by subdividing these chapters.

All contributing causes of death. At the chapter level we found a significantly increased mortality among KS subjects with infectious, neurological, circulatory, pulmonary, and urinary tract diseases as primary or contributing causes of death. Subdividing infectious and pulmonary diseases, we found an increased risk of dying with septicemia, pneumonia, and nonasthmatic obstructive airway disease as the primary or contributing cause of death (Table 2).

Diagnoses of special interest due to previous findings are shown in Table 3. Contrary to the previous studies, we did not find significantly increased mortality from any cancer, diabetes mellitus, cerebrovascular diseases, diseases of the digestive system, or intestinal thrombosis.

FIG. 1. Survival of KS subjects *vs.* control subjects (hazard ratio, 1.40; 95% CI, 1.13–1.74; $P = 0.002$). KS subjects lost 2.1 yr (95% CI, 0.3–3.9 yr; median survival) compared with control subjects.

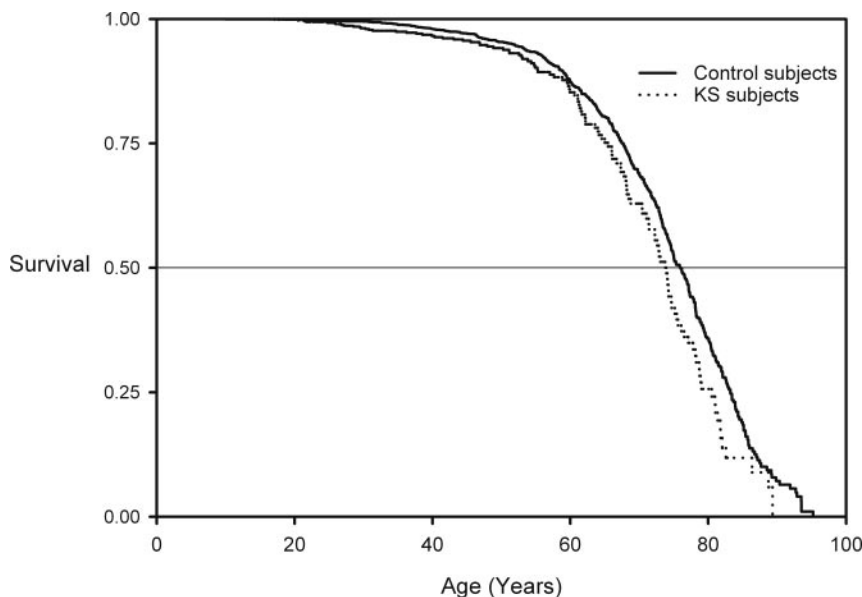


TABLE 1. Relative mortality, by main diagnostic groups

Diagnostic group	Primary cause of death		All contributing causes of death	
	No. of deaths KS/controls	Hazard ratio (95% CI)	No. of deaths KS/controls	Hazard ratio (95% CI)
Infectious and parasitic diseases	3/2	7.18 (1.20–43.0) ^a	6/10	3.95 (1.25–12.5) ^a
Neoplasms	23/137	0.97 (0.61–1.54)	28/154	1.10 (0.72–1.68)
Diseases of the blood and blood-forming organs and immune system	0/0	^b	1/1	^b
Endocrine, nutritional and metabolic diseases	2/8	1.47 (0.27–8.12)	10/37	1.80 (0.83–3.92)
Mental and behavioural disorders	0/6	^b	17/63	1.45 (0.81–2.55)
Diseases of the nervous system, eye, and ear	2/6	2.52 (0.41–15.5)	7/15	3.62 (1.24–10.5) ^a
Diseases of the circulatory system	39/181	1.33 (0.91–1.95)	59/253	1.41 (1.03–1.93) ^a
Diseases of the respiratory system	19/31	3.51 (1.77–7.00) ^c	36/87	2.97 (1.88–4.71) ^c
Diseases of the digestive system	7/18	1.71 (0.59–4.99)	9/36	1.31 (0.58–2.93)
Diseases of the skin and sc tissue	0/1	^b	0/5	^b
Diseases of the musculoskeletal system and connective tissue	0/0	^b	2/6	0.95 (0.18–5.14)
Diseases of the genitourinary system	6/5	5.20 (1.43–19.0) ^a	7/13	4.30 (1.41–13.1) ^a
Congenital malformations ^d	5/1	15.0 (1.56–144) ^c	21/1	79.4 (10.6–596) ^c
Symptoms, signs, and abnormal clinical and laboratory findings	2/17	0.52 (0.12–2.34)	2/19	0.49 (0.11–2.20)
Injury, poisoning, and certain other consequences of external causes	13/61	1.66 (0.63–2.16)	16/65	1.34 (0.76–2.36)
Uncertain death diagnosis	1/9	1.21 (0.12–12.1)		
No information available	2/8	1.70 (0.33–8.78)		

^a $P < 0.05$.^b Due to few events, no estimate was calculated.^c $P < 0.001$.^d Including KS as a cause of death.**TABLE 2.** Causes of death (all contributing causes) with significant differences

Diagnosis	Hazard ratio	CI	<i>P</i>	No. of deaths
Infections	3.95	1.25–12.5	0.020	6/10
<i>Septicemia</i>	6.64	1.17–37.6	0.031	4/5
Neurological diseases	3.62	1.24–10.6	0.018	7/15
Circulatory diseases	1.41	1.03–1.93	0.030	59/253
Lung diseases	2.97	1.88–4.71	0.000	35/87
<i>Pneumonia</i>	2.25	1.20–4.21	0.011	18/49
<i>Chronic obstructive airway disease</i>	3.16	1.51–6.59	0.002	15/38
Genitourinary diseases	4.30	1.41–13.1	0.010	7/13
Natural death	1.47	1.16–1.86	0.001	109/417
Suicide	2.24	0.96–5.25	0.062	7/16

If a significant hazard ratio was found in a given chapter; analysis of chapter subgroups was made (shown in *italics*). Only significant Hazard ratios are shown.

Impact of karyotype on mortality

Karyotypes were subdivided into three groups; the first group included karyotype XXY, the second the mosaic karyotypes (XY/XXY), and the third group included karyotypes with more than one extra X chromosome, *i.e.* XXXY and XXXXY (Table 4). Two of the groups were small, and there was no significant difference in mortality among the three groups (data not shown).

Manner of death

We found a significantly increased mortality risk from dying of natural causes. There was a nonsignificantly increased risk of dying from suicide, but no differences in mortality risk from accidents. There was one death due to homicide among the control subjects.

Discussion

In this study KS was associated with an increased mortality of 40% and a reduction in median survival of 2.1 yr

(95% CI, 0.3–3.9 yr), compared with an age-matched control group, corroborating findings from previous studies (5, 6). The mortality was increased for most causes, and it was significantly increased for infectious, neurological, circulatory, pulmonary, and urinary tract diseases. We could not, however, confirm earlier findings of increased mortality due to breast cancer and cerebrovascular diseases (Table 3).

Discrepancies between our findings and those of previous studies could be explained in part by differences in design. We used the same register of causes of death to describe the mortality in both groups. Data from the Danish Register of Causes of Death are not perfect; there is a tendency for common causes of death, *e.g.* myocardial infarction, to be overdiagnosed and rare causes, such as cerebral hemorrhage and intestinal thrombosis, to be underdiagnosed (17), but we have no reason to believe that the risk of misclassification is different for KS subjects and others. The two previous studies were both performed in the United Kingdom, and differences in frequency and practices in performing autopsies may also influence the findings of the more rare causes of death.

TABLE 3. Cause-specific mortality ratios from the study by Swerdlow *et al.* (4) and the present study

Cause/disease	Swerdlow <i>et al.</i> (4)		Our findings	
	Relative risk	No. of deaths	Hazard ratio (95% CI)	No. of deaths KS/controls
Lung cancer	2.45 (1.55–3.67)	23	1.22 (0.55–2.72)	8/40
Breast cancer	61.7 (7.47–223)	2	^a	0/0
Diabetes mellitus	7.07 (2.60–15.4)	6	1.64 (0.66–4.07)	7/30
Circulatory disease	1.41 (1.09–1.81)	65	1.41 (1.03–1.93) ^b	59/253
Cerebrovascular diseases	2.31 (1.37–3.65)	18	0.78 (0.35–1.73)	5/39
Respiratory diseases	2.24 (1.44–3.32)	24	2.97 (1.88–4.71) ^b	36/87
Pneumonia	2.92 (1.46–5.22)	11	2.24 (1.20–4.21) ^b	18/49
Diseases of the digestive system	2.57 (1.03–5.30)	7	1.31 (0.58–2.93)	9/36
Intestinal thrombosis	17.0 (3.49–49.5)	3	^a	1/1

^a Due to few events, no estimate was calculated.^b $P < 0.05$.**TABLE 4.** Karyotype distribution in the KS subjects from the final cohort

Karyotype	No. (%)
47,XXY	698 (89.4)
Mosaics (46,XY/47,XXY)	53 (6.8)
Supranumeric (48,XXXY, 49,XXXXY)	29 (3.7)
Concomitant trisomy	1 (0.1)
Total	781 (100)

The percentage of the total is given in parentheses.

Using an age-matched control group enabled us not only to analyze the primary cause of death, but also to include contributing causes of death in our analyses. As an example, a subject suffering from diabetes, which rarely is a primary cause of death, may die from myocardial infarction, but diabetes is still a contributing cause of death.

The hypogonadism found in KS could lead to an increased mortality from diabetes and atherosclerosis, because of its association with abdominal adiposity (18–20). In contrast, one could speculate that testosterone treatment could lead to an increased mortality from atherosclerosis because of its possible deleterious effect on lipid profile (21) and prostate cancers. However, we found no significantly increased mortality from any cancer, diabetes, or ischemic heart disease. Excess smoking or an elevated sensitivity to tobacco smoke might explain the increased mortality from nonasthmatic obstructive airway disease, but, in contrast, no excess mortality from lung cancer was found. Cerebral hemorrhage has previously been described as a major cause of death in KS (5, 6), but our data do not support this association; in fact, we found an insignificantly reduced risk.

The increased risk of dying from cardiovascular diseases could in part be explained by the previous findings of Fricke *et al.* (12), who reported an increased incidence of mitral valve prolapse, a condition associated with an increased risk of sudden death (22, 23). We found no deaths from mitral valve prolapse.

The risk of cancer in KS has been studied previously in a Danish register study. Hasle *et al.* (24) used the Danish Cancer Registry to study cancer incidence, but not mortality. They found the same overall cancer incidence in KS subjects and the background population, with an increased risk of mediastinal germ cell tumors only (25). The results from that study, published in 1995, are supported by those of the

present study using registers independent of the Danish Cancer Registry.

The karyotypes 48,XXXY and 49,XXXXY are associated with a more severely affected phenotype, with lower intelligence and increased risk of malformations (26). Swerdlow *et al.* (5) found a nonsignificantly increased mortality risk among KS with three or more X chromosomes; thus, an increased mortality risk could be expected. There were only 29 subjects with these karyotypes in our study, and we could not demonstrate an increased mortality among them.

Mosaic KS may be associated with a less affected phenotype (27, 28), but information on their morbidity or mortality is lacking, largely due to the small numbers of subjects. We did not find any decreased or increased mortality in the rather small population of mosaic KS (60 subjects).

We found an insignificantly increased risk of dying from suicide. This could be related to psychological and psychiatric distress among men suffering from KS (3, 28) as well as from the fact that many are less well educated (3) and thus more exposed to unemployment and social isolation.

Only approximately one fourth of men suffering from KS are diagnosed, at least in Denmark (2) and the United Kingdom (4), and most are diagnosed beyond puberty; the remaining 75% are unknown. Different diagnostic avenues may lead to the diagnosis of KS. In prepubertal boys, the stigmata of the syndrome are mild, and most boys diagnosed early may suffer from learning disabilities. As puberty develops, the lack of proper masculinization and of growth of the testes may lead to the diagnosis. In early adulthood the most frequent problem leading to diagnosis is infertility (4). Later in life, comorbidity, such as osteoporosis, diabetes, and autoimmune diseases, may lead to the diagnosis. Diagnosed men with KS may therefore represent the worst and best ends of the spectrum, and those who do not show enough stigmata to be diagnosed early and do not present themselves in the infertility clinic may not be diagnosed. Because we currently have no clear picture of the status of the group of nondiagnosed men with KS, our results cannot be extrapolated to this group. They may differ in many aspects from those diagnosed with KS.

The strengths of the present study are that this is a nationwide register study, covering all diagnosed KS subjects in Denmark, performed in a uniform public health care system with complete long-term follow-up. By including an age-matched control group, we were able to adjust for the

changing mortality during the decades we were investigating. Furthermore, the design made it possible to analyze not only the primary cause of death, but also contributing causes of death, which are omitted in traditional analysis of mortality.

The limitations of this study are mainly due to the lack of clinical data for the subjects. Neither the Danish Cytogenetic Central Register nor the Danish Register of Causes of Death incorporates any clinical data or data regarding phenotype. The study does not allow determining to what extent the increased mortality among men diagnosed with KS is a direct biological effect of the syndrome *per se* or of hypogonadism and to what extent it is due to unfavorable socioeconomic conditions and lifestyle. However, the moderately increased mortality from many different causes points to the latter interpretation.

Acknowledgments

Received May 3, 2004. Accepted June 8, 2004.

Address all correspondence and requests for reprints to: Dr. Anders Bojesen, Medical Department M. (Diabetes and Endocrinology), Aarhus Sygehus, Aarhus University Hospital, Noerrebrogade 42–44, DK-8000 Aarhus C, Denmark. E-mail: anders.bojesen@dadlnet.dk.

This work was supported by Grant 9600822 from the Danish Health Research Council (Aarhus University-Novo Nordisk Center for Research in Growth and Regeneration). A.B. received a Ph.D. research fellowship from University of Aarhus.

References

- Nielsen J, Wohler M 1990 Sex chromosome abnormalities found among 34,910 newborn children: results from a 13-year incidence study in Arhus, Denmark. *Birth Defects Orig Article Ser* 26:209–223
- 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
- Ratcliffe S 1999 Long-term outcome in children of sex chromosome abnormalities. *Arch Dis Child* 80:192–195
- Abramsky L, Chapple J 1997 47,XXY (Klinefelter syndrome) and 47,XY: estimated rates of and indication for postnatal diagnosis with implications for prenatal counselling. *Prenat Diagn* 17:363–368
- 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
- Price WH, Clayton JE, 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
- 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
- van den Bergh JP, Hermus AR, Spruyt AI, Sweep CG, Corstens FH, Smals AG 2001 Bone mineral density and quantitative ultrasound parameters in patients with Klinefelter's syndrome after long-term testosterone substitution. *Osteop Int* 12:55–62
- Horowitz M, Wishart JM, O'Loughlin PD, Morris HA, Need AG, Nordin BE 1992 Osteoporosis and Klinefelter's syndrome. *Clin Endocrinol (Oxf)* 36:113–118
- Wong FH, Pun KK, Wang C 1993 Loss of bone mass in patients with Klinefelter's syndrome despite sufficient testosterone replacement. *Osteop Int* 3:3–7
- Kubler A, Schulz G, Cordes U, Beyer J, Krause U 1992 The influence of testosterone substitution on bone mineral density in patients with Klinefelter's syndrome. *Exp Clin Endocrinol* 100:129–132
- Fricke GR, Mattern HJ, Schweikert HU 1981 Mitral valve prolapse in Klinefelter syndrome. *Lancet* 2:1414
- Oktenli C, Yesilova Z, Kocar IH, Musabak U, Ozata M, Inal A, Gul D, Sanisoglu Y 2002 Study of autoimmunity in Klinefelter's syndrome and idiopathic hypogonadotropic hypogonadism. *J Clin Immunol* 22:137–143
- Miyagawa S, Matsuura E, Kitamura W, Ohno H, Kichikawa K, Uchida H, Shirai T, Okamoto S 1995 Systemic lupus erythematosus and anticardiolipin antibodies in Klinefelter's syndrome. *Lupus* 4:236–238
- Gravholt CH, Juul S, Naeraa RW, Hansen J 1998 Morbidity in Turner syndrome. *J Clin Epidemiol* 51:147–158
- Juel K, Helweg-Larsen K 1999 The Danish registers of causes of death. *Dan Med Bull* 46:354–357
- Mabeck CE, Wichmann B 1980 Causes of death and death certificates. An evaluation of the diagnosis in 373 death certificates. *Ugeskr Laeger* 142:257–261
- Tsai EC, Boyko EJ, Leonetti DL, Fujimoto WY 2000 Low serum testosterone level as a predictor of increased visceral fat in Japanese-American men. *Int J Obes Relat Metab Disord* 24:485–491
- Cefalu WT, Wang ZQ, Werbel S, Bell-Farrow A, Crouse JR, Hinson WH, Terry JG, Anderson R 1995 Contribution of visceral fat mass to the insulin resistance of aging. *Metabolism* 44:954–959
- Abate N, Haffner SM, Garg A, Peshock RM, Grundy SM 2002 Sex steroid hormones, upper body obesity, and insulin resistance. *J Clin Endocrinol Metab* 87:4522–4527
- Jones DB, Higgins B, Billet JS, Price WH, Edwards CR, Beastall GH, Shepherd J, Sweeting VM, Horn DB, Wenham PR 1989 The effect of testosterone replacement on plasma lipids and apolipoproteins. *Eur J Clin Invest* 19:438–441
- Davies MJ, Moore BP, Braimbridge MV 1978 The floppy mitral valve. Study of incidence, pathology, and complications in surgical, necropsy, and forensic material. *Br Heart J* 40:468–481
- Devereux RB, Kramer-Fox R, Shear MK, Kligfield P, Pini R, Savage DD 1987 Diagnosis and classification of severity of mitral valve prolapse: methodologic, biologic, and prognostic considerations. *Am Heart J* 113:1265–1280
- Storm HH, Michelsen EV, Clemmensen IH, Pihl J 1997 The Danish cancer registry: history, content, quality and use. *Dan Med Bull* 44:535–539
- Hasle H, Mellemegaard A, Nielsen J, Hansen J 1995 Cancer incidence in men with Klinefelter syndrome. *Br J Cancer* 71:416–420
- Visootsak J, Aylstock M, Graham Jr JM 2001 Klinefelter syndrome and its variants: an update and review for the primary pediatrician. *Clin Pediatr* 40:639–651
- Sarkar R, Marimuthu KM 1983 Association between the degree of mosaicism and the severity of syndrome in Turner mosaics and Klinefelter mosaics. *Clin Genet* 24:420–428
- Smyth CM, Bremner WJ 1998 Klinefelter syndrome. *Arch Intern Med* 158:1309–1314