REVIEW

Morbidity, mortality, and socioeconomics in Klinefelter syndrome and 47,XYY syndrome: a comparative review

Lukas Ochsner Ridder[1,2], Agnethe Berglund[2,3], Kirstine Stochholm[1], Simon Chang[1,4] and Claus H Gravholt[1,2,4]

[1]Department of Endocrinology and Internal Medicine and Medical Research Laboratories, Aarhus University Hospital, Aarhus, Denmark
[2]Department of Molecular Medicine, Aarhus University Hospital, Aarhus, Denmark
[3]Department of Clinical Genetics and Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark
[4]Unit for Thrombosis Research, Hospital of South West Jutland and University of Southern Denmark, Esbjerg, Denmark

Correspondence should be addressed to C Gravholt: claus.gravholt@clin.au.dk

Abstract

Context: Klinefelter syndrome (KS, 47,XXY) and 47,XYY syndrome are genetic conditions characterized by a supernumerary sex chromosome. The conditions share many traits, but considerable phenotypic differences are seen between the two. Focusing on morbidity, mortality, and socioeconomics, this review highlights similarities and differences.

Methods: Relevant literature was identified through PubMed with the following search terms; 'Klinefelter', '47,XXY', '47,XYY', and 'Jacobs syndrome'. Included journal articles were chosen at the authors' discretion.

Results: KS and 47,XYY are the most common sex chromosome disorders in males, with an expected prevalence of 152 and 98 per 100,000 newborn males, respectively. Non-diagnosis is extensive, as only about 38% of KS and 18% of 47,XYY are diagnosed. Both conditions are associated with an increased mortality risk and increased risk of a variety of diseases and other health-related problems affecting virtually every organ system. Early diagnosis seems to predict a lesser comorbidity burden. Neurocognitive deficits as well as social and behavioral problems are commonly described. Both syndromes are associated with poor socioeconomic for example, lower income and educational level and higher rates of crime. Infertility is a hallmark of KS, but fertility seems also reduced in 47,XYY.

Conclusion: Being born as a boy with an extra X or Y chromosome is associated with increased mortality and excess morbidity, partially expressed in a sex chromosome-specific pattern. Both syndromes continue to be greatly underdiagnosed, even though early intervention may improve the overall outcome. Earlier diagnosis to initiate timely counseling and treatment should be emphasized.

Key Words

- Klinefelter syndrome
- Jacobs syndrome
- 47,XYY
- morbidity
- mortality

Endocrine Connections (2023) **12**, **e230024**

Introduction

Klinefelter syndrome (KS) and 47,XYY syndrome are two distinct common sex chromosome abnormalities sharing some known similarities. KS is comparatively well described, where plentiful studies have expanded our knowledge during recent years, especially concerning the natural course during adulthood. Knowledge concerning 47,XYY syndrome is much more limited. Here, we review the similarities and differences between KS and XYY.

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-23-0024

Diagnosis and epidemiology of male supernumerary sex chromosome abnormalities

The prevalence of KS has been estimated to be 57 per 100,000 in newborn males, perhaps with an increasing incidence over the last 50 years (1). Other studies found an adult prevalence ranging from 11 to 34/100,000 men in the diagnosed population. Previous cytogenetic surveys have found an expected prevalence of 152/100,000 men. The main reason for the discrepancy is that only about 38% of expected KS patients are diagnosed (1, 2, 3). The prevalence of diagnosed 47,XYY in the Danish population has been increasing in the last 50 years (1). Much like KS, 47,XYY is underdiagnosed with a prevalence of 3–9/100,000 in diagnosed populations. In newborns, 47,XYY were found in 18/100,000 boys, corresponding to 18% of the expected 98/100,000 found in cytogenetic surveys (1, 2). A recent study from the UK Biobank study among 207,067 males showed that only 49 of 213 (23%) KS males and 1 of 143 (0.7%) 47,XYY males were diagnosed, but indeed presented with comorbidity closely matching those males with a known diagnosis of either KS or 47,XYY syndrome (4).

The median age of diagnosis is 27.5 years among KS compared to 15.1 years in 47,XYY. Among KS there is an increasing diagnostic rate at age 25–35 years, most likely related to consultations in fertility clinics. The fertility rate among 47,XYY is higher than in KS, likely resulting in the identification of fewer cases through young adult years.

An estimated 87% of KS patients have the 47,XXY karyotype, while the remaining 13% have a variety of mosaic karyotypes. Considering the varied phenotype of KS and that conducted studies may only include the most symptomatic KS cases, it is difficult to make specific recommendations for diagnostic criteria that include all ranges of KS phenotypes. The European Academy of Andrology guidelines on Klinefelter Syndrome recommends that all patients with primary hypogonadism, increased levels of gonadotropins and testis volume < 5 mL, as well as patients with non-obstructive severe oligozoospermia, should have karyotype analysis to exclude or confirm KS. Boys with cryptorchidism without spontaneous descent within a year should be screened for KS (5).

The continued underdiagnosis of KS and 47,XYY point toward a structural problem in modern health care and perhaps the implementation of better screening methods, involvement of school nurses, and general information about the syndrome could lead to more KS and 47,XYY males being diagnosed earlier, increasing the likelihood of receiving correct treatment and clinical care. For general practitioners, physical examination is important, since small testes, increased height, and low hemoglobin in otherwise healthy males should lead to further investigation for KS. Suspecting 47,XYY from physical examination alone is more difficult due to less abnormal differences compared to normal males; however, flat feet, knee valgus, and clinodactyli are more frequent in 47,XYY.

Morbidity and mortality in Klinefelter syndrome

Increased morbidity and mortality are well described in KS. Hypergonadotropic hypogonadism is one of the most frequent issues in KS patients, resulting in infertility and accelerating metabolic syndrome, with 90–100% of KS patients having elevated gonadotropins (follicle-stimulating hormone, luteinizing hormone) and 65–85% of KS patients having decreased testosterone levels (6). KS patients may have signs of hypogonadism regardless of testosterone levels within the normal range. Even though current guidelines suggest that only KS with low testosterone should receive testosterone replacement therapy (TRT), we suggest that elevated gonadotropins in KS should result in consideration of TRT regardless of testosterone levels (Fig. 1).

Endocrine diseases with autoimmune components are seen more frequently in KS patients compared to men from the background population. The risk of hypothyroidism is about three-fold increased, while the risk of Addison's disease is about twelve-fold (7), and the risk of type 1 diabetes is two-fold and type 2 diabetes is about four-fold increased (8, 9).

Other autoimmune diseases are observed more frequently in KS males compared to controls and the pathophysiology is still unclear, but the diseases seen more frequently in KS males resemble the autoimmune disease pattern typically found in women (9). In KS, conditions like multiple sclerosis (relative risk (RR): 4.3), rheumatoid arthritis (RR: 3.3), Sjögren's syndrome (RR: 19.3), and systemic lupus erythematosus (RR 18.1), as well as inclusion body myositis, polymyositis/dermatomyositis, and systemic sclerosis are seen more frequently (10). Exceptions are autoimmune diseases like ankylosing spondylitis and Goodpasture's disease, which are not seen more frequently among KS males (7). A likely explanation

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-23-0024

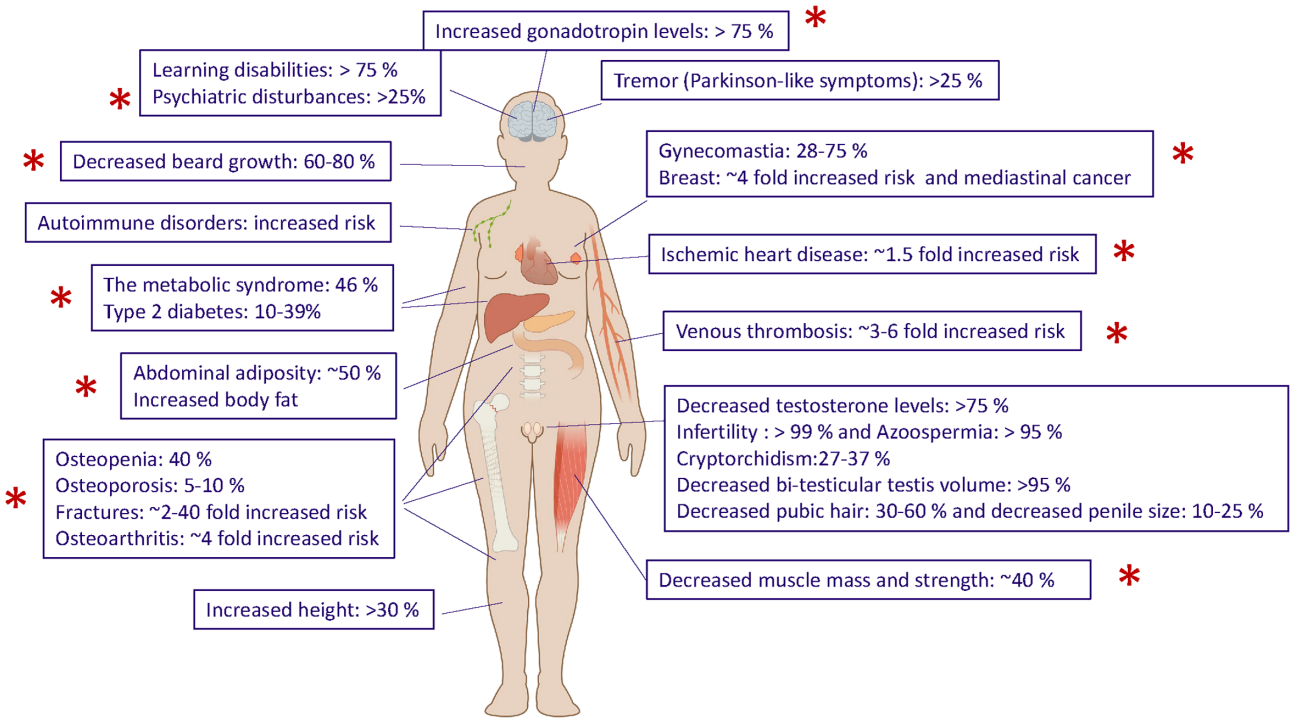

Figure 1
Abnormalities and diseases in KS males. *Testosterone may possibly positively impact several features of KS (12).

could be the extra X-chromosome mimicking the genome of 46,XX women.

KS males are known to have impaired bone metabolism, reduced bone mass density (BMD) (11), and a prevalence of osteoporosis of 5–10% and approximately 40% for osteopenia (12). Relative or manifest hypogonadism and a higher prevalence of metabolic syndrome are some factors that potentially decrease BMD. A Danish registry study found an eight-fold increased risk of osteoporosis and a 1.4-fold increased risk of fractures (8). Assessing BMD using high-resolution peripheral quantitative computed tomography shows reduced bone parameters compared to controls (13). One study found vertebral fractures were more likely in KS patients diagnosed after the age of 21 compared to those diagnosed before the age of 21, regardless of BMD (14). Di Nisio *et al*. found an inverse relationship between the Leydig-specific marker insulin-like 3 peptide (INSL3) and sclerostin, a protein involved in bone catabolism. INSL3, which has an anabolic effect on bone, is reduced in KS patients and is associated with reduced lumbar and femoral BMD in patients with osteoporosis (15).

Studies have found that treated KS patients have higher lumbar BMD than non-treated KS patients and found direct negative effects of age of diagnosis and body composition on the trabecular bone score and risk of vertebral fractures (16). The duration of testosterone treatment is linked to improved body composition (17, 18). The administration route of testosterone, transdermal vs injection, is in a 5-year observational study assessed as equally effective in terms of metabolic parameters and BMD (19); however, proper randomized studies are needed to fully appreciate possible differences in the route of administration of testosterone. Vogiatzi *et al*. conducted a randomized controlled trial study that showed increased bone health index in KS boys aged 5–10 years with the administration of oxandrolone, an anabolic steroid, over a 2-year period (20).

Taken together, this indicates that bone metabolism is impaired in KS patients due to hypogonadism, body composition, and possibly the chromosome abnormality in itself. Higher rates of osteoporosis and fractures require a focus on early diagnosis and sufficient androgen treatment to likely improve bone strength and reduce fracture risk.

When KS was first described by Harry Klinefelter in 1942, it was associated with gynecomastia (21). A later epidemiological study found a hazard ratio (HR) of 34.8 for gynecomastia in KS compared with 46,XY males. Studies have found the prevalence of gynecomastia between 24

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-23-0024

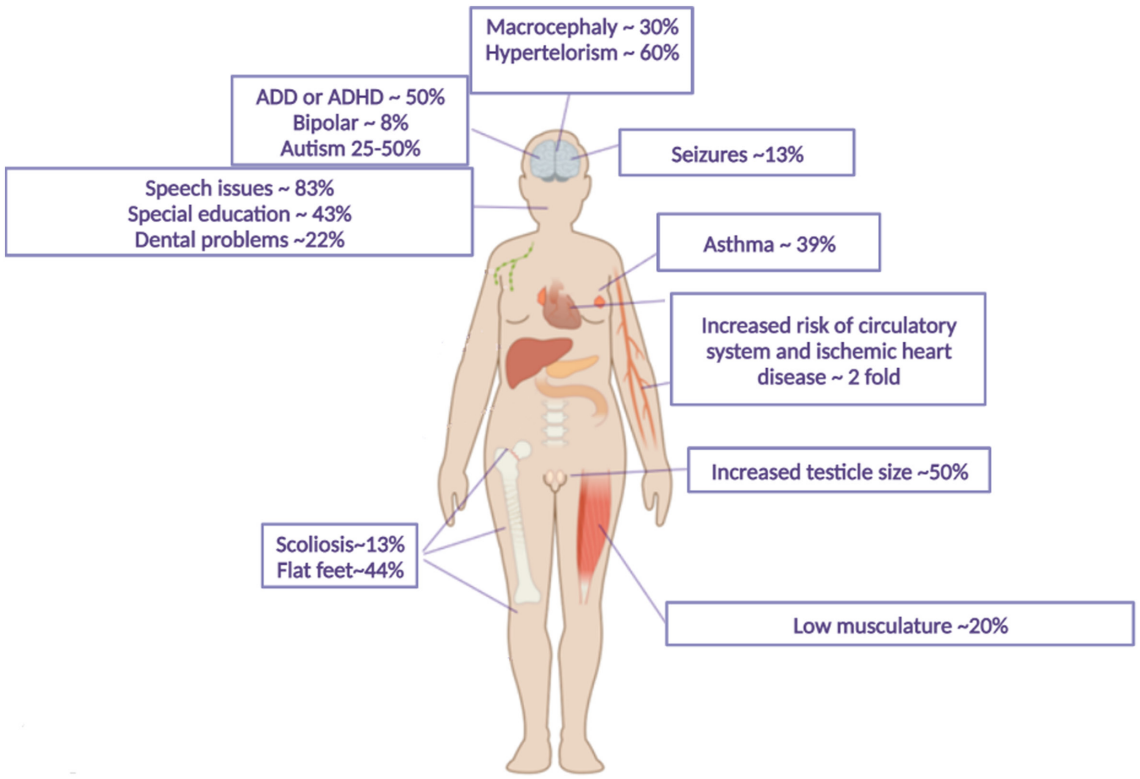

Figure 2
Abnormalities and diseases present in 47,XYY males (32, 36, 90, 91).

and 70% in KS, with the prevalence influenced by the definition of gynecomastia and how well physicians diagnose it (22). A UK study from 2021 on adolescent KS and controls found no difference in the incidence of gynecomastia, 35.6 vs 34.0%, respectively (23). However, the frequency of gynecomastia is quite low in hospital discharge diagnoses (8), amounting to 4.4% among KS and 0.15% among controls. The KS phenotype varies greatly as well as the level of hypogonadism. KS patients who are not treated sufficiently with testosterone likely present with gynecomastia more often.

Congenital malformations are more frequent in KS, with malformations of the heart occurring five-fold more frequent, malformations of the genitalia being five-fold more frequent, and retention of testes being six-fold more frequent (8). Swerdlow *et al.* studied 3518 KS patients and also found a seven-fold increased mortality standardized mortality ratio (SMR) due to congenital anomalies.

Extra-gonadal germ cell tumors (GCTs) are 19 times more frequent in KS than in other males (24). Some recommend that all patients with GCT are screened for KS since 33% of GCT patients have KS (25), and this seems to be a prudent suggestion. Gonadal germ-cell neoplasia has not been observed more frequently in KS, only extra-gonadal GCTs derived from somatic cells are more frequent in KS (26). Based on KS prevalence among breast cancer patients, it is estimated that KS patients have a 50-fold increase in breast cancer rates and a SMR of 57.8. Especially in mosaic KS patients, breast cancer seems to be increased (27). However, since the absolute risk of breast cancer is very low in the male background population, the absolute risk of breast cancer among KS males is not sufficiently high to warrant systematic examination. Prostate cancer is less frequent in KS patients (27). Non-Hodgkin lymphoma is found with increased frequency in KS patients in two studies (27, 28). Solid tumors seem to be less frequent than among controls (27). However, results on cancer risk in KS are conflicting since the diagnosis of KS patients is incomplete, and the true risk of cancer in the entire KS population remains unknown (Table 1). The overall cancer risk seems to be similar to that of the background population.

Research has indicated that androgen receptor insensitivity may play role in the phenotype in individuals with KS. CAGn repeats, which are linked to specific phenotypic traits such as gynecomastia, reduced bone density, testicular size, body height as well as education, time of diagnosis, and stable partnership (29).

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-23-0024

Table 1 Cancer risk in males with KS.

	UK data(27)	**Danish data** (9, 88, 92)	**Swedish data** (28, 93)
All malignancies	**SMR: 1.2 (1.0–1.4)**	**HR: 1.33 (1.03–1.72)** RR: 1.1 (0.8–1.5)	SIR: 0.87 (0.66–1.12)
Breast cancer	**SMR: 57.8 (18.8–135.0)**		RR: 49 SIR: 4.37 (0.00–25.03)
Prostate cancer	SMR: 0 (0–0.7) SIR: 0.2 (0.02–07)		SIR: 0.24 (0.06–0.61)
Non-Hodgkin lymphoma	**SMR: 3.5 (1.6–6.6)** SIR: 2.0 (0.8–3.9)		**SIR: 3.02 (1.44–5.57)**
Haematological malignancy			**SIR: 2.72 (1.61–4.30)**
Solid tumors			**SIR: 0.66 (0.47–0.90)**
Leukemia	SMR:1.7 (0.5–4.3)		**SIR: 3.62 (1.30–7.93)**
Lung	**SMR: 1.5 (1.0–2.0)** **SIR: 1.4 (1.0–1.9)**	RR: 1.6 (0.7–3.0) HR: 1.22 (0.55–2.72)	SIR: 1.16 (0.46–2.41)

Significant results are in bold.
HR, hazard ratio (95% CI); RR, relative risk (95% CI); SIR, standardized incidence ratio (95% CI); SMR, standardized mortality ratio (95% CI).

However, other research has not confirmed this association and questions the importance of androgen receptor insensitivity in KS (30), and it is safe to say that larger studies will be needed to resolve this issue.

Morbidity and mortality in 47,XYY syndrome

While numerous studies have highlighted an increased disease risk in KS, only a few studies have reported on the risk of comorbidity in 47,XYY syndrome. Current literature is dominated by case reports and a few small single-center cross-sectional studies, and in many cases, no major medical problems are present. However, population-based studies from the UK and Denmark have reported a two- to three-fold increase in overall mortality in 47,XYY compared to the general population (31, 32) and a more than two-fold increase in overall morbidity (33). In addition, 19% of men with 47,XYY report poor overall health and far more (63%) long-standing illness or infirmity(4) – stressing a need for much more focus on long-term health outcomes in boys and men with 47,XYY syndrome.

As in KS, 47,XYY syndrome males probably have an increased risk of congenital malformations (Fig. 2). Disregarding minor malformations including flat feet, knee valgus, and clinodactyly, all commonly described features of 47,XYY syndrome (34, 35, 36), malformations are typically not reported in relation to XYY. However, evaluating causes of death in males with polysomy Y, Higgins *et al.* reported increased mortality due to congenital malformations (32), and evaluating in- and outpatient hospital diagnoses in the Danish 47,XYY cohort, we found a significantly increased risk of malformations related to the circulatory system, although without any clear pattern of specific malformations (33). Data from the UK Biobank showed a significant association between 47,XYY and spina bifida (4). As discussed elsewhere in this review, it is well-known that KS and Turner syndrome (45,X) (37, 38) are associated with an increased risk of a range of autoimmune diseases, whereas, to our knowledge, no such associations have been reported for 47,XYY. Recently, however, Howell *et al.* aimed to investigate for an association between eosinophilic esophagitis, an autoimmune esophageal disease characterized by an increased number of eosinophils in the esophagus and symptoms of esophageal dysfunction (38), and conditions with supernumerary sex chromosomes. The results were a higher than expected rate of feeding difficulties and gastroesophageal among their patients (39). Out of 71 youngsters with 47,XYY, 4 were diagnosed with eosinophilic esophagitis (1 per 18 47,XYY), suggesting a substantially higher risk than in the general pediatric population (39). Treatment for eosinophilic esophagitis can include proton pump inhibitors. Interestingly, investigating prescribed medication among 47,XYY and age-matched general population male controls, we found 47,XYY males to have a significantly increased risk of being prescribed medication for acid-related disorders (33), although the study was unable to draw any conclusions on the reason for this increased prescription rate.

Assessing 92 boys with 47,XYY at a mean age of 9.6 years, Bardsley *et al.* found that most boys were of relatively normal weight, but there was a trend toward central adiposity (36). In contrast, adult 47,XYY men participating in the UK Biobank were found to have higher body mass index (BMI) and a higher percentage of total body fat than 46,XY men as well as lower levels of high-density

lipoprotein (HDL), higher levels of triglycerides, and a significantly increased risk of type 2 diabetes and obesity (4) – all pointing toward an association between 47,XYY syndrome and an unfavorable body composition with a negatively altered metabolic profile.

Compared to the general population, mortality in 47,XYY due to pulmonary disease is increased five- to ten-fold (31, 32), and asthma has been reported as a frequent feature of 47,XYY syndrome (36, 40). 47,XYY men in the UK Biobank had significantly lower forced expiratory volumes than their 46,XY counterparts and a significantly increased risk of asthma (20% of 47,XYY vs 12% of 46,XY) (4). In comparison, in the Danish 47,XYY cohort, 17% had a hospital contact related to asthma and 4% had at least one contact related to chronic obstructive pulmonary disease, both corresponding to an incidence rate ratio of nearly six, when compared to controls (33). These findings were confirmed by a significantly increased risk of prescriptions for obstructive lung disease among 47,XYY men (33).

Neurocognition, socioeconomy, and crime

It is a clinical observation that not only do many men with KS or 47,XYY have problems with assessing the job market and keeping a job, but already in the classroom many boys with KS or 47,XYY struggle. This seems to translate to affected socioeconomic status. However, the causes are manifold and not fully uncovered.

Learning and intellectual disabilities, using the Differential Abilities Scale, were seen in 82 boys with KS compared with 50 control boys with a mean age of 9 years (41). A follow-up study on 19 KS boys ascertained as newborns in a cytogenetic survey described that most KS men have less skilled jobs than their fathers, but without an increase in unemployment (42). Further, autism traits were significantly higher across all dimensions for the autism phenotype in 31 men with KS compared to 20 control men from the background population, whereas there was no difference in intellectual ability (43). In another study investigating personality traits, anxiety, and depression, 69 men with KS were compared with male controls matched for age and years of education. Here, anxiety and depression symptoms were markedly increased in KS, and neuroticism was identified as having a central role (44). In the same two groups, the frequency distribution of scores on autism spectrum quotient subscales was shown (45). Men with KS scored lower on attention switching, imagination, communication, and social skills compared to controls, with no difference in attention-to-detail scores. Moreover, men with KS have difficulties in visuospatial processing, face recognition, and in recognition of facial expression when investigated using the Amsterdam Neuropschychological Tasks program (46).

As these neurocognitive challenges affect not only the early years of schooling and education, a challenged socioeconomic status in many men with KS must be anticipated. A national study on 1049 KS men showed a reduced level of education, fewer achieving fatherhood and fewer attaining marital status, lower income throughout the lifespan, and an increased level of retirement compared to age-matched general population controls (47).

Whether social management training in KS men is an effective tool to improve social, emotional, and behavioral functioning is not thoroughly investigated. A recent study of 16 men with KS showed no change in the frequency of engagement in social behavior or overall distress during social interaction after neurocognitive intervention (48). However, attention problems and externalizing behavior such as aggressive behavior and rule-breaking behavior decreased in KS from the pretest to the posttest. Similarly, anxious and depressed behavior decreased significantly.

Regardless, the need for evidence-based treatment programs in KS is evident no matter the age of the individual. In the same context, it is noteworthy, that compared to Down syndrome, available information on the internet describes KS as a genetic and gendered syndrome with physical, developmental, and infertility issues, whereas Down syndrome is described as a syndrome with opportunities without prominently addressing physical and health symptoms. This leaves parents of boys with KS with less hope, a factor which is associated with worse coping and adaptation (49).

Very few scientific studies concerning criminality and KS are published. The area is controversial; however, without sound evidence, this sensitive topic cannot be addressed and appropriately affected. In 2018, a review aiming to identify prevalence data on KS and criminality identified only one study not conducted in a prison or a hospital, namely a national study on crime in all diagnosed Danish men with KS (50). In brief, we found an increased risk of being convicted in men with KS compared to age-matched men. The only exception was conviction due to traffic offenses, which was significantly reduced. Overall, the increased risk of being convicted was normalized when adjusting for socioeconomic

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-23-0024

profile, not counting arson and sexual abuse (50). Similar results have been found for 47,XYY with a slightly higher HR for convictions other than traffic offenses compared to age matched men and compared to KS (51). There was a remarkably increased risk of being incarcerated due to arson among both KS and 47,XYY males.

As seen in KS, 47,XYY males are known to be less likely to cohabitate, become fathers, receive an education, and are more likely to go become retired (2). A Danish registry study found that 47,XYY males would cohabitate 5 years later than controls (49). At 30 years of age, 11.4% of 47,XYY have education compared to 29.0% in controls (49); another Danish registry study found similar results, with an HR of education of 0.35 in 47,XYY compared to controls (2, 52). Early retirement is more likely in 47,XYY when compared to controls and also compared to KS males. Early retirement is more likely after receiving a supernumerary sex chromosome abnormality (SCA) diagnosis, indicating less opportunities or easier acceptance of early retirement (2).

Income is seen reduced in 47,XYY in all stages of life (52). Reasons for a reduced educational level and reduced income remain unclear. The intelligence quotient (IQ), in particular verbal IQ, is reduced in 47,XYY, whereas performance IQ may be reduced; however, results are not conclusive (53). One study compared 47,XYY boys with age-matched controls and found alterations in gray and white matter volume similar to KS patients using magnetic resonance imaging, yet very dissimilar from Turner syndrome patients. The structural changes in the brain of supernumerary SCA males may be linked to the cognitive difficulties in patients with supernumerary SCAs, but this has not been conclusively shown (54).

Autism spectrum disease (ASD) is, as in KS, increased in 47,XYY with approximately one out of five receiving an ASD diagnosis (55). With learning difficulties, most 47,XYY require support in the early years, yet some manage to get an education without any assistance. One study compared two cohorts of 47,XYY – one with postnatal diagnosis and one with prenatal diagnosis. The prenatal diagnosis group showed higher verbal IQ, performance IQ, and full-scale IQ, as well as better social interaction and communication skills underlining the importance of early diagnosis and relevant information for parents and physicians, but probably also indirectly showing that children diagnosed postnatally with 47,XYY are more phenotypically affected or increased parental resources are present among children prenatally diagnosed (36).

We presume that early diagnosis would yield a more optimal situation, making it possible for the trained clinician to elucidate for the parents the possible challenges for many of the boys with supernumerary SCA. Balancing between not stigmatizing the individual, and introducing the possible social and neurocognitive deficits in boys with supernumerary sex chromosomes, not only parents and family but also their kindergarten teachers and teachers, in general, can most likely improve their efforts in helping boys with supernumerary sex chromosomes. Hopefully, boys with supernumerary sex chromosomes might improve their learning abilities

Table 2 Similarities and differences in males with KS and 47,XYY.

Klinefelter syndrome (47,XXY)	**47,XYY males**
Differences	
Tall with narrow shoulders, altered body composition and lower muscle mass	*Tall*, but probably normal body composition
Increased risk of several autoimmune diseases	Increased acid reflux and eosinophil esophagitis
Impaired bone metabolism and increased risk of fractures	No indication of impaired bone metabolism
Azoospermia and infertility	Varying testicular function
Almost all have hypergonadotropic hypogonadism	Decreased fertility and reduced likelihood to father children than normal males
Similarities	
Increased height	
Increased truncal fat mass and BMI	
Gynecomastia and erectile dysfunction	
Increased CVD risk and risk of VTE	
Decreased socioeconomic status, increased rates of autism, decreased verbal intelligence, and increased crime rates	
Generally increased morbidity due to a multitude of different causes	
Increased mortality due to congenital malformations	
Increased risk of metabolic syndrome	
Increased risk of cancer mortality	
Poorer socioeconomic status	

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-23-0024

and general quality of life with an individualized and pedagogical approach. Mainly in KS, questions whether testosterone substitution initiated at the relevant time during puberty, or later, can alter the socioeconomic status is still unaccounted for. Randomized trials on the timing of diagnosis and age of testosterone treatment seem unethical, although studies aiming at elucidating whether either early or late pubertal addition of testosterone is optimal, would be ethical. Observational studies on differences in outcomes related to the time of diagnosis might be flawed as early diagnoses often is a consequence of more severe phenotypes (51).

Testicular function and fertility in 47,XYY syndrome

In contrast to KS where testicular dysfunction and infertility is a hallmark, the impact on the testicular function of an extra Y chromosome is much less appreciated (Table 2). Historically, there has been an impression of the 47,XYY syndrome as a 'super male' syndrome with robust testicular function, likely because the first studies of men with 47,XYY were carried out in penal institutions for aggressive and anti-social behavior (56) and reported increased levels of testosterone in 47,XYY (57, 58). However, there have been numerous reports of adult men with 47,XYY and oligozoo- or azoospermic sperm counts, not rarely in addition to hypergonadotropic hypogonadism (59,60, 61), and 47,XYY men have shown to be more prevalent in infertile populations than in the general population (59, 62, 63). In a nationwide population-based study including all men diagnosed with 47,XYY in Denmark for almost 50 years, we found that 47,XYY men were much less likely to father a child compared to general population controls (52). Similar findings were recently reported in a UK Biobank study (4).Out of 143 men with 47,XYY aged 40–70 years, more than half were childless, which was significantly more than the 21% of men with standard male karyotype (4). Interestingly, the authors found an apparently normal testicular function in 47,XYY men compared to 46,XY men as no significant difference in pubertal timing and testosterone level was observed (4). This contrasts with Danish epidemiological data showing a significantly increased occurrence of infertility and gonadal dysfunction in 47,XYY men compared to controls, in addition to a significantly increased risk of being prescribed androgens, indirectly pointing toward testicular failure among many with 47,XYY. The Danish data also show an increased occurrence of gynecomastia, cryptorchidism, and erectile dysfunction in 47,XYY – all substantiating an increased prevalence of testicular dysfunction compared to age-matched general population male controls (33). It can be speculated whether the different findings in these two studies rely on the fundamental difference between the UK Biobank data and the Danish data; where the UK Biobank require active participation with a risk of healthy volunteer bias (64) – highlighted by the fact that only 1 out of the 143 men had been diagnosed with 47,XYY clinically (4), the Danish data are based on patients karyotyped on the clinicians' discretion, thus potentially more likely to represent 47,XYY men at the more severe end of the phenotypic spectrum. Interestingly, however, among 82 47,XYY boys, whereof half had been diagnosed prenatally, most often as an incidental finding because of advanced maternal age screening, Davis *et al.* found evidence of impaired testicular function in 47,XYY already during childhood – with no difference between pre- and postnatally diagnosed boys. Using measures of inhibin B and anti-Müllerian hormone (AMH) as a measure of testicular function, the authors reported a blunted rise in inhibin B in 47,XYY in early puberty compared to controls, and prepubertal 47,XYY boys had higher levels of AMH than prepubertal controls – likely explained by lower intratesticular testosterone concentrations or relative resistance to testosterone (65). Testosterone levels did however not differ between 47,XYY and controls (65). Rather than concluding this to be a reflection of normal testicular function, the authors instead suggest that testosterone has lower sensitivity for estimating testicular function in 47,XYY, especially prepubertally (65).

Taken together, 47,XYY syndrome appears associated with varying testicular function, and impairment seems more prevalent than previously anticipated. There is a need for future studies to focus on testicular function in 47,XYY and its underlying mechanisms.

Cardiovascular disease

Cardiovascular disease (CVD) is a concern in both KS and 47,XYY (Table 2). The syndromes are both associated with increased mortality risk and a reduced life span, with a large proportion of the excess mortality explained by an increased incidence of diseases of the circulatory system (12, 66, 67). For instance, men with KS present an up to eight-fold increased risk of death due to venous

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-23-0024

thromboembolisms (VTEs) compared to the male background population (68). The underlying mechanism driving the excess risk is far from elucidated. This inhibits the ability of clinicians in guiding patients concerning individual risk assessment, application of CVD prophylactic measures and choices regarding treatment of incident CVD.

Generally accepted commonly acquired risk factors for VTE include malignancy, major surgery or trauma, and obesity (69, 70, 71). Established major risk factors for arterial thrombotic events (ATE) such as myocardial infarction include hypertension, high blood concentration of low-density lipoprotein (LDL), low blood concentration of HDL, glucose intolerance or diabetes, and smoking (72). Adding to this, atrial arrhythmia is a major risk factor for stroke and transient ischemic attacks (73, 74).

Incidence of the above risk factors has been mostly investigated in KS and to a lesser extent in 47,XYY. Overall, as discussed earlier, KS is not associated with an increased risk of cancer, although individual types of cancer are more frequent (12). Based on observational data from Danish national registries, the incidence of a first major surgery per 10,000 person-years was 163.2 in KS and 133.0 in the male background population yielding an HR of 1.39 (95% confidence interval, 1.29–1.49) (unpublished observation). Similarly, Danish registry data yield a higher rate of first hospitalization for trauma in KS compared with men in the background population (HR (95% CI), 1.58 (1.38–1.79) (8). There are no available data describing rates of recurrent surgery or trauma in KS. Obesity and higher rates of diabetes and metabolic syndrome are well-established traits in KS (9, 12), and for any given BMI men with KS present with increased abdominal fat mass compared with control males (75). These metabolic changes seem to be present early in life among boys with KS, and a large number of men and boys with KS present with an unfavorable lipid profile – increased levels of LDL and low levels of HDL (12, 75, 76, 77) and men with KS have a higher risk of being treated with cholesterol-lowering medications (68). Similarly, Danish registry data find higher rates of hypertension, atrial fibrillation, angina pectoris, and arteriosclerosis in men with KS compared with the male background population with concomitant increased rates of prescriptions for antihypertensive medications, anticoagulation therapy, and platelet inhibitors (68). Comparably, 47,XYY has been associated with increased rates of obesity in a large register study (33), while an older observational study on hypertension found no difference between 47,XYY and matched controls (78). However, in the aforementioned register study, 47,XYY was associated with higher rates of prescriptions for medications in the ATC code C (cardiovascular system) including diuretics (33), with data on other common antihypertensive medications (ATC code C07, C08, and C09) not given specifically.

Interestingly, we now have data from the UK biobank finding similarly increased markers of cardiovascular risk in undiagnosed KS and 47,XYY (4), including higher risk of type 2 diabetes, arteriosclerosis, and reduced HDL in both groups. These data support the notion of cardiovascular risk indeed being an intrinsic complication of these syndromes.

As indicated by the excessive presence of cardiovascular risk factors in KS and 47,XYY, epidemiological studies from different countries have been able to establish a markedly increased risk of VTE among these patient populations (4, 33, 67, 68, 79, 80). Similarly, a marked increased risk of ATE would be expected, but the epidemiological data are less clear in this regard. We saw no difference in the risk of ATE in our most recent epidemiological study comparing men with KS and men in the Danish background population (68), but men with KS did have a higher risk of ATE-related death. Similarly, our recent register-based study on 47,XYY somewhat surprisingly revealed a reduced risk of ischemic heart disease among the patients (33). The background for this apparent paradox of an attenuated ATE risk in KS and 47,XYY is unknown. It is very likely that other factors including specific genetic modifications are contributing significantly as modifiers of CVD risk in KS and 47,XYY. As such, commonly applied CVD risk prediction algorithms, for example the Framingham Risk Score and SCORE2, might not be applicable in these conditions. Future studies accessing genetic and epigenetic traits associable with CVD risk in KS and 47,XYY could further be of interest as an overall model of genetic risk modification in CVD.

Both KS and to some extent 47,XYY present with hypogonadism that in itself could indicate an increased CVD risk, with a potential benefit from TRT (81, 82, 83). There are no data on the effects of TRT on CVD risk in 47,XYY. Data from the Danish registries comparing treated and untreated KS indicate a protective effect of TRT on VTE risk in KS, but the finding was non-significant (68). Similarly, observational studies investigating hemostatic traits such as platelet aggregation, coagulation, and fibrinolysis, have not been able to show significant beneficial or detrimental effects of TRT in KS (84, 85, 86,

87). As such, the potential of TRT in ultimately reducing CVD risk in KS and 47,XYY is still debatable (17).

The only guideline on the treatment of KS currently available advocates attention to prophylaxis and treatment of cardiovascular risk factors in KS, including education on lifestyle and yearly assessment of weight, waist circumference, blood pressure, fasting glucose, HbA1c, and lipid profile (5). Further, in the guideline, it is suggested to treat thrombosis prophylaxis prior to long-haul flights or exposure to other risks in patients with KS to attenuate the increased risk for deep vein thrombosis and/or pulmonary embolism (5). Both men with KS and 47,XYY have higher hospital admittance rates compared with controls (33, 88) and VTE prophylaxis in relation to hospitalization should be strongly considered, based on an individual risk assessment. This is in line with the American Society of Hematology 2018 guidelines for VTE prophylaxis (89) considering, however, that the efficacy of thromboprophylactic medication in KS has not been studied specifically and that the evidence supporting the general recommendations in the guideline are of low quality. Studies are also needed to elucidate the efficacy of general treatment protocols for VTE and ATE in KS and 47,XYY to establish guidelines, for instance, describing the duration of anticoagulation therapy following VTE, etc.

We conclude that both KS and 47,XYY syndrome show many similarities in relation to the occurrence of metabolic conditions, such as type 2 diabetes, an unfavorable lipid profile, body compositional changes, and arteriosclerosis. Increased specific cancer rates are best described in KS males but increased mortality due to cancer may also be present in 47,XYY. Altered neurocognitive functions resulting in poorer socioeconomic conditions are also shared, as well as increased crime rates. Autoimmune disease in general seems more prevalent in KS males than 47,XYY whereas acid reflux and eosinophil esophagitis are more dominant in 47,XYY. KS males have impaired bone metabolism, which has not been found in 47,XYY; however, studies investigating this are sparse. There are specific traits such as almost universal hypogonadism and infertility among KS males, but also some males with 47,XYY seem to be affected by these traits. No dominant trait separates 47,XYY from KS, it seems that the KS and 47,XYY share many of the same phenotypical traits, but with differences in frequency. More studies are needed to investigate how these phenotypical traits arise and how KS and 47,XYY have partly overlapping phenotype yet different genotype.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

C.H.G. was supported by Novo Nordisk Foundation (NNF15OC0016474, NNF20OC0060610), 'Fonden til lægevidenskabens fremme', the Familien Hede Nielsen foundation and the Independent Research Fund Denmark (0134-00406A).

Acknowledgements

Claus H Gravholt and Kirstine Stochholm are members of the European Reference Network on Rare Endocrine Conditions (ENDO-ERN), Project ID number 739543.

References

1 Berglund A, Viuff MH, Skakkebæk A, Chang S, Stochholm K & Gravholt CH. Changes in the cohort composition of turner syndrome and severe non-diagnosis of Klinefelter, 47,XXX and 47,XYY syndrome: a nationwide cohort study. *Orphanet Journal of Rare Diseases* 2019 **14** 16. (https://doi.org/10.1186/s13023-018-0976-2)

2 Berglund A, Stochholm K & Gravholt CH. The epidemiology of sex chromosome abnormalities. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics* 2020 **184** 202–215. (https://doi.org/10.1002/ajmg.c.31805)

3 Coffee B, Keith K, Albizua I, Malone T, Mowrey J, Sherman SL & Warren ST. Incidence of fragile X syndrome by newborn screening for methylated FMR1 DNA. *American Journal of Human Genetics* 2009 **85** 503–514. (https://doi.org/10.1016/j.ajhg.2009.09.007)

4 Zhao Y, Gardner EJ, Tuke MA, Zhang H, Pietzner M, Koprulu M, Jia RY, Ruth KS, Wood AR, Beaumont RN, *et al.* Detection and characterization of male sex chromosome abnormalities in the UK Biobank study. *Genetics in Medicine* 2022 **24** 1909–1919. (https://doi.org/10.1016/j.gim.2022.05.011)

5 Zitzmann M, Aksglaede L, Corona G, Isidori AM, Juul A, T'Sjoen G, Kliesch S, D'Hauwers K, Toppari J, Słowikowska-Hilczer J, *et al.* European academy of andrology guidelines on Klinefelter Syndrome Endorsing Organization: European Society of Endocrinology. *Andrology* 2021 **9** 145–167. (https://doi.org/10.1111/andr.12909)

6 Smyth CM & Bremner WJ. Klinefelter syndrome. *Archives of Internal Medicine* 1998 **158** 1309–1314. (https://doi.org/10.1001/archinte.158.12.1309)

7 Gravholt CH, Chang S, Wallentin M, Fedder J, Moore P & Skakkebæk A. Klinefelter syndrome: integrating genetics, neuropsychology, and endocrinology. *Endocrine Reviews* 2018 **39** 389–423. (https://doi.org/10.1210/er.2017-00212)

8 Seminog OO, Seminog AB, Yeates D & Goldacre MJ. Associations between Klinefelter's syndrome and autoimmune diseases: English national record linkage studies. *Autoimmunity* 2015 **48** 125–128. (https://doi.org/10.3109/08916934.2014.968918)

9 Bojesen A, Juul S, Birkebaek NH & Gravholt CH. Morbidity in Klinefelter syndrome: a Danish register study based on hospital discharge diagnoses. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 1254–1260. (https://doi.org/10.1210/jc.2005-0697)

10 Falhammar H, Claahsen-van der Grinten H, Reisch N, Slowikowska-Hilczer J, Nordenström A, Roehle R, Bouvattier C, Kreukels BPC, Köhler B & dsd-LIFE group. Health status in 1040 adults with disorders of sex development (DSD): a European multicenter study. *Endocrine Connections* 2018 **7** 466–478. (https://doi.org/10.1530/EC-18-0031)

11 Scofield RH, Lewis VM, Cavitt J, Kurien BT, Assassi S, Martin J, Gorlova O, Gregersen P, Lee A, Rider LG, *et al.* 47XXY and 47XXX in Scleroderma and myositis. *ACR Open Rheumatology* 2022 **4** 528–533. (https://doi.org/10.1002/acr2.11413)

12 Bojesen A, Birkebæk N, Kristensen K, Heickendorff L, Mosekilde L, Christiansen JS & Gravholt CH. Bone mineral density in Klinefelter syndrome is reduced and primarily determined by muscle strength and resorptive markers, but not directly by testosterone. *Osteoporosis International* 2011 **22** 1441–1450. (https://doi.org/10.1007/s00198-010-1354-7)

13 Shanbhogue VV, Hansen S, Jørgensen NR, Brixen K & Gravholt CH. Bone geometry, volumetric density, microarchitecture, and estimated bone strength assessed by HR-pQCT in Klinefelter syndrome. *Journal of Bone and Mineral Research* 2014 **29** 2474–2482. (https://doi.org/10.1002/jbmr.2272)

14 Vena W, Pizzocaro A, Indirli R, Amer M, Maffezzoni F, Delbarba A, Leonardi L, Balzarini L, Ulivieri FM, Ferlin A, *et al.* Prevalence and determinants of radiological vertebral fractures in patients with Klinefelter syndrome. *Andrology* 2020 **8** 1699–1704. (https://doi.org/10.1111/andr.12841)

15 Di Nisio A, De Toni L, Rocca MS, Ghezzi M, Selice R, Taglialavoro G, Ferlin A & Foresta C. Negative association between sclerostin and INSL3 in isolated human osteocytes and in Klinefelter syndrome: new hints for testis-bone crosstalk. *Journal of Clinical Endocrinology and Metabolism* 2018 **103** 2033–2041. (https://doi.org/10.1210/jc.2017-02762)

16 Vena W, Carrone F, Delbarba A, Akpojiyovbi O, Pezzaioli LC, Facondo P, Cappelli C, Leonardi L, Balzarini L, Farina D, *et al.* Body composition, trabecular bone score and vertebral fractures in subjects with Klinefelter syndrome. *Journal of Endocrinological Investigation* 2023 **46** 297–304. (https://doi.org/10.1007/s40618-022-01901-8)

17 Pizzocaro A, Vena W, Condorelli R, Radicioni A, Rastrelli G, Pasquali D, Selice R, Ferlin A, Foresta C, Jannini EA, *et al.* Testosterone treatment in male patients with Klinefelter syndrome: a systematic review and meta-analysis. *Journal of Endocrinological Investigation* 2020 **43** 1675–1687. (https://doi.org/10.1007/s40618-020-01299-1)

18 Tahani N, Nieddu L, Prossomariti G, Spaziani M, Granato S, Carlomagno F, Anzuini A, Lenzi A, Radicioni AF & Romagnoli E. Long-term effect of testosterone replacement therapy on bone in hypogonadal men with Klinefelter syndrome. *Endocrine* 2018 **61** 327–335. (https://doi.org/10.1007/s12020-018-1604-6)

19 Kabilan A, Skakkebæk A, Chang S & Gravholt CH. Evaluation of the efficacy of transdermal and injection testosterone therapy in Klinefelter syndrome: a real-life study. *Journal of the Endocrine Society* 2021 **5** bvab062. (https://doi.org/10.1210/jendso/bvab062)

20 Vogiatzi MG, Davis SM & Ross JL. Cortical bone mass is low in boys with Klinefelter syndrome and improves with oxandrolone. *Journal of the Endocrine Society* 2021 **5** bvab016. (https://doi.org/10.1210/jendso/bvab016)

21 Klinefelter HF, Reifenstein EC & Albright F. Syndrome characterized by gynecomastia, aspermatogenesis without A-Leydigism, and increased excretion of follicle-stimulating Hormone1. *Journal of Clinical Endocrinology and Metabolism* 1942 **2** 615–627. (https://doi.org/10.1210/jcem-2-11-615)

22 Johnson RE & Murad MH. Gynecomastia: pathophysiology, evaluation, and management. *Mayo Clinic Proceedings* 2009 **84** 1010–1015. (https://doi.org/10.1016/S0025-6196(11)60671-X)

23 Butler G. Incidence of gynaecomastia in Klinefelter syndrome adolescents and outcome of testosterone treatment. *European Journal of Pediatrics* 2021 **180** 3201–3207. (https://doi.org/10.1007/s00431-021-04083-2)

24 Williams LA, Pankratz N, Lane J, Krailo M, Roesler M, Richardson M, Frazier AL, Amatruda JF & Poynter JN. Klinefelter syndrome in males with germ cell tumors: A report from the Children's Oncology Group. *Cancer* 2018 **124** 3900–3908. (https://doi.org/10.1002/cncr.31667)

25 Rojas AP, Vo DV, Mwangi L, Rehman S & Peiris AN. Oncologic manifestations of Klinefelter syndrome. *Hormones (Athens)* 2020 **19** 497–504. (https://doi.org/10.1007/s42000-020-00241-7)

26 Slowikowska-Hilczer J, Szarras-Czapnik M, Duranteau L, Rapp M, Walczak-Jedrzejowska R, Marchlewska K, Oszukowska E, Nordenstrom A & DSD-LIFE Group. Risk of gonadal neoplasia in patients with disorders/differences of sex development. *Cancer Epidemiology* 2020 **69** 101800. (https://doi.org/10.1016/j.canep.2020.101800)

27 Swerdlow AJ, Schoemaker MJ, Higgins CD, Wright AF, Jacobs PA & UK Clinical Cytogenetics Group. Cancer incidence and mortality in men with Klinefelter syndrome: a cohort study. *Journal of the National Cancer Institute* 2005 **97** 1204–1210. (https://doi.org/10.1093/jnci/dji240)

28 Ji J, Zöller B, Sundquist J & Sundquist K. Risk of solid tumors and hematological malignancy in persons with Turner and Klinefelter syndromes: a national cohort study. *International Journal of Cancer* 2016 **139** 754–758. (https://doi.org/10.1002/ijc.30126)

29 Zitzmann M, Depenbusch M, Gromoll J & Nieschlag E. X-chromosome inactivation patterns and androgen receptor functionality influence phenotype and social characteristics as well as pharmacogenetics of testosterone therapy in Klinefelter patients. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 6208–6217. (https://doi.org/10.1210/jc.2004-1424)

30 Bojesen A, Hertz JM & Gravholt CH. Genotype and phenotype in Klinefelter syndrome - impact of androgen receptor polymorphism and skewed X inactivation. *International Journal of Andrology* 2011 **34** e642–e648. (https://doi.org/10.1111/j.1365-2605.2011.01223.x)

31 Stochholm K, Juul S & Gravholt CH. Diagnosis and mortality in 47,XYY persons: a registry study. *Orphanet Journal of Rare Diseases* 2010 **5** 15. (https://doi.org/10.1186/1750-1172-5-15)

32 Higgins CD, Swerdlow AJ, Schoemaker MJ, Wright AF, Jacobs PA & UK Clinical Cytogenetics Group. Mortality and cancer incidence in males with Y polysomy in Britain: a cohort study. *Human Genetics* 2007 **121** 691–696. (https://doi.org/10.1007/s00439-007-0365-8)

33 Berglund A, Stochholm K & Gravholt CH. Morbidity in 47,XYY syndrome: a nationwide epidemiological study of hospital diagnoses and medication use. *Genetics in Medicine* 2020 **22** 1542–1551. (https://doi.org/10.1038/s41436-020-0837-y)

34 Parker CE, Melyk J & Fish CH. The XYY syndrome. *American Journal of Medicine* 1969 **47** 801–808. (https://doi.org/10.1016/0002-9343(69)90173-9)

35 Cordeiro L, Tartaglia N, Roeltgen D & Ross J. Social deficits in male children and adolescents with sex chromosome aneuploidy: a comparison of XXY, XYY, and XXYY syndromes. *Research in Developmental Disabilities* 2012 **33** 1254–1263. (https://doi.org/10.1016/j.ridd.2012.02.013)

36 Bardsley MZ, Kowal K, Levy C, Gosek A, Ayari N, Tartaglia N, Lahlou N, Winder B, Grimes S & Ross JL. 47,XYY syndrome: clinical phenotype and timing of ascertainment. *Journal of Pediatrics* 2013 **163** 1085–1094. (https://doi.org/10.1016/j.jpeds.2013.05.037)

37 Berglund A, Cleemann L, Oftedal BE, Holm K, Husebye ES & Gravholt CH. 21-hydroxylase autoantibodies are more prevalent in Turner syndrome but without an association to the autoimmune polyendocrine syndrome type I. *Clinical and Experimental Immunology* 2019 **195** 364–368. (https://doi.org/10.1111/cei.13231)

38 Gravholt CH, Juul S, Naeraa RW & Hansen J. Morbidity in Turner syndrome. *Journal of Clinical Epidemiology* 1998 **51** 147–158. (https://doi.org/10.1016/s0895-4356(97)00237-0)

39 Howell S, Buchanan C, Davis SM, Miyazawa H, Furuta GT, Tartaglia NR & Nguyen N. Eosinophilic esophagitis in individuals with sex chromosome aneuploidies: clinical presentations and management implications. *Molecular Genetics and Genomic Medicine* 2021 **9** e1833. (https://doi.org/10.1002/mgg3.1833)

40 Bender BG, Puck MH, Salbenblatt JA & Robinson A. The development of four unselected 47,XYY boys. *Clinical Genetics* 1984 **25** 435–445. (https://doi.org/10.1111/j.1399-0004.1984.tb02013.x)

41 Ross JL, Roeltgen DP, Kushner H, Zinn AR, Reiss A, Bardsley MZ, McCauley E & Tartaglia N. Behavioral and social phenotypes in boys with 47,XYY syndrome or 47,XXY Klinefelter syndrome. *Pediatrics* 2012 **129** 769–778. (https://doi.org/10.1542/peds.2011-0719)

42 Ratcliffe S. Long-term outcome in children of sex chromosome abnormalities. *Archives of Disease in Childhood* 1999 **80** 192–195. (https://doi.org/10.1136/adc.80.2.192)

43 van Rijn S, Swaab H, Aleman A & Kahn RS. Social behavior and autism traits in a sex chromosomal disorder: Klinefelter (47XXY) syndrome. *Journal of Autism and Developmental Disorders* 2008 **38** 1634–1641. (https://doi.org/10.1007/s10803-008-0542-1)

44 Skakkebæk A, Moore PJ, Pedersen AD, Bojesen A, Kristensen MK, Fedder J, Hertz JM, Østergaard JR, Wallentin M & Gravholt CH. Anxiety and depression in Klinefelter syndrome: the impact of personality and social engagement. *PLoS One* 2018 **13** e0206932. (https://doi.org/10.1371/journal.pone.0206932)

45 Skakkebæk A, Moore PJ, Pedersen AD, Bojesen A, Kristensen MK, Fedder J, Laurberg P, Hertz JM, Østergaard JR, Wallentin M, *et al.* The role of genes, intelligence, personality, and social engagement in cognitive performance in Klinefelter syndrome. *Brain and Behavior* 2017 **7** e00645. (https://doi.org/10.1002/brb3.645)

46 van Rijn S, de Sonneville L & Swaab H. The nature of social cognitive deficits in children and adults with Klinefelter syndrome (47,XXY). *Genes, Brain, and Behavior* 2018 **17** e12465. (https://doi.org/10.1111/gbb.12465)

47 Bojesen A, Stochholm K, Juul S & Gravholt CH. Socioeconomic trajectories affect mortality in Klinefelter syndrome. *Journal of Clinical Endocrinology and Metabolism* 2011 **96** 2098–2104. (https://doi.org/10.1210/jc.2011-0367)

48 Martin F, van Rijn S, Bierman M & Swaab H. Social management training in males with 47,XXY (Klinefelter syndrome): a pilot study of a neurocognitive-behavioral treatment targeting social, emotional, and behavioral problems. *American Journal on Intellectual and Developmental Disabilities* 2021 **126** 1–13. (https://doi.org/10.1352/1944-7558-126.1.1)

49 Liu XS, Tumolo M & Biedendorf J. Content analysis of social support, and disease framing of Klinefelter syndrome and Down syndrome: social support, framing and decision tendencies. *Health Communication* 2021 **38** 1–10. (https://doi.org/10.1080/10410236.2021.1976949)

50 O'Donovan R & Völlm B. Klinefelter's syndrome and sexual offending: a literature review. *Criminal Behaviour and Mental Health* 2018 **28** 132–140. (https://doi.org/10.1002/cbm.2052)

51 Stochholm K, Bojesen A, Jensen AS, Juul S & Gravholt CH. Criminality in men with Klinefelter's syndrome and XYY syndrome: a cohort study. *BMJ Open* 2012 **2** e000650. (https://doi.org/10.1136/bmjopen-2011-000650)

52 Stochholm K, Juul S & Gravholt CH. Socio-economic factors affect mortality in 47,XYY syndrome-A comparison with the background population and Klinefelter syndrome. *American Journal of Medical Genetics. Part A* 2012 **158A** 2421–2429. (https://doi.org/10.1002/ajmg.a.35539)

53 Leggett V, Jacobs P, Nation K, Scerif G & Bishop DV. Neurocognitive outcomes of individuals with a sex chromosome trisomy: XXX, XYY, or XXY: a systematic review. *Developmental Medicine and Child Neurology* 2010 **52** 119–129. (https://doi.org/10.1111/j.1469-8749.2009.03545.x)

54 Lepage JF, Hong DS, Raman M, Marzelli M, Roeltgen DP, Lai S, Ross J & Reiss AL. Brain morphology in children with 47,XYY syndrome: a voxel- and surface-based morphometric study. *Genes, Brain, and Behavior* 2014 **13** 127–134. (https://doi.org/10.1111/gbb.12107)

55 Bishop DVM, Jacobs PA, Lachlan K, Wellesley D, Barnicoat A, Boyd PA, Fryer A, Middlemiss P, Smithson S, Metcalfe K, *et al.* Autism, language and communication in children with sex chromosome trisomies. *Archives of Disease in Childhood* 2011 **96** 954–959. (https://doi.org/10.1136/adc.2009.179747)

56 Jacobs PA, Brunton M, Melville MM, Brittain RP & McClemont WF. Aggressive behavior, mental sub-normality and the XYY male. *Nature* 1965 **208** 1351–1352. (https://doi.org/10.1038/2081351a0)

57 Schiavi RC, Theilgaard A, Owen DR & White D. Sex chromosome anomalies, hormones, and aggressivity. *Archives of General Psychiatry* 1984 **41** 93–99. (https://doi.org/10.1001/archpsyc.1984.01790120097012)

58 Price WH & van der Molen HJ. Plasma testosterone levels in males with the 47,XYY karyotype. *Journal of Endocrinology* 1970 **47** 117–122. (https://doi.org/10.1677/joe.0.0470117)

59 El-Dahtory F & Elsheikha HM. Male infertility related to an aberrant karyotype, 47,XYY: four case reports. *Cases Journal* 2009 **2** 28. (https://doi.org/10.1186/1757-1626-2-28)

60 Zhang X, Liu X, Xi Q, Zhu H, Li L, Liu R & Yu Y. Reproductive outcomes of 3 infertile males with XYY syndrome: retrospective case series and literature review. *Medicine (Baltimore)* 2020 **99** e19375. (https://doi.org/10.1097/MD.0000000000019375)

61 Kim IW, Khadilkar AC, Ko EY & Sabanegh ES, Jr. 47,XYY syndrome and male infertility. *Reviews in Urology* 2013 **15** 188–196.

62 Borjian Boroujeni P, Sabbaghian M, Vosough Dizaji A, Zarei Moradi S, Almadani N, Mohammadpour Lashkari F, Zamanian MR & Mohseni Meybodi A. Clinical aspects of infertile 47,XYY patients: a retrospective study. *Human Fertility* 2019 **22** 88–93. (https://doi.org/10.1080/14647273.2017.1353143)

63 Yoshida A, Miura K & Shirai M. Cytogenetic survey of 1,007 infertile males. *Urologia Internationalis* 1997 **58** 166–176. (https://doi.org/10.1159/000282975)

64 Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, Collins R & Allen NE. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. *American Journal of Epidemiology* 2017 **186** 1026–1034. (https://doi.org/10.1093/aje/kwx246)

65 Davis SM, Bloy L, Roberts TPL, Kowal K, Alston A, Tahsin A, Truxon A & Ross JL. Testicular function in boys with 47,XYY and relationship to phenotype. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics* 2020 **184** 371–385. (https://doi.org/10.1002/ajmg.c.31790)

66 Swerdlow AJ, Hermon C, Jacobs PA, Alberman E, Beral V, Daker M, Fordyce A & Youings S. Mortality and cancer incidence in persons with numerical sex chromosome abnormalities: a cohort study. *Annals of Human Genetics* 2001 **65** 177–188. (https://doi.org/10.1017/S0003480001008569)

67 Swerdlow AJ, Higgins CD, Schoemaker MJ, Wright AF, Jacobs PA & United Kingdom Clinical Cytogenetics Group. Mortality in patients with Klinefelter syndrome in Britain: a cohort study. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 6516–6522. (https://doi.org/10.1210/jc.2005-1077)

68 Chang S, Christiansen CF, Bojesen A, Juul S, Munster AB & Gravholt CH. Klinefelter syndrome and testosterone treatment: a national cohort study on thrombosis risk. *Endocrine Connections* 2020 **9** 34–43. (https://doi.org/10.1530/EC-19-0433)

69 Lijfering WM, Rosendaal FR & Cannegieter SC. Risk factors for venous thrombosis - current understanding from an epidemiological point of view. *British Journal of Haematology* 2010 **149** 824–833. (https://doi.org/10.1111/j.1365-2141.2010.08206.x)

70 Anderson FA, Jr & Spencer FA. Risk factors for venous thromboembolism. *Circulation* 2003 **107**(Supplement 1) I9–I16. (https://doi.org/10.1161/01.CIR.0000078469.07362.E6)

71 Goldhaber SZ. Risk factors for venous thromboembolism. *Journal of the American College of Cardiology* 2010 **56** 1–7. (https://doi.org/10.1016/j.jacc.2010.01.057)

72 Vasan RS, Sullivan LM, Wilson PW, Sempos CT, Sundstrom J, Kannel WB, Levy D & D'Agostino RB. Relative importance of borderline and elevated levels of coronary heart disease risk factors. *Annals of Internal Medicine* 2005 **142** 393–402. (https://doi.org/10.7326/0003-4819-142-6-200503150-00005)

73 Grysiewicz RA, Thomas K & Pandey DK. Epidemiology of ischemic and hemorrhagic stroke: incidence, prevalence, mortality, and risk factors. *Neurologic Clinics* 2008 **26** 871–895, vii. (https://doi.org/10.1016/j.ncl.2008.07.003)

74 O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, Rao-Melacini P, Zhang X, Pais P, Agapay S, *et al.* Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet* 2016 **388** 761–775. (https://doi.org/10.1016/S0140-6736(16)30506-2)

75 Chang S, Skakkeaek A, Trolle C, Bojesen A, Hertz JM, Cohen A, Hougaard DM, Wallentin M, Pedersen AD, Ostergaard JR, *et al.* Anthropometry in Klinefelter syndrome - multifactorial influences due to CAG length, testosterone treatment and possibly intrauterine hypogonadism. *Journal of Clinical Endocrinology and Metabolism* 2015 **100** E508–E517. (https://doi.org/10.1210/jc.2014-2834)

76 Aksglaede L, Molgaard C, Skakkebaek NE & Juul A. Normal bone mineral content but unfavourable muscle/fat ratio in Klinefelter syndrome. *Archives of Disease in Childhood* 2008 **93** 30–34. (https://doi.org/10.1136/adc.2007.120675)

77 Bardsley MZ, Falkner B, Kowal K & Ross JL. Insulin resistance and metabolic syndrome in prepubertal boys with Klinefelter syndrome. *Acta Paediatrica* 2011 **100** 866–870. (https://doi.org/10.1111/j.1651-2227.2011.02161.x)

78 Boisen E, Owen DR, Rasmussen L & Sergeant J. Cardiac functioning and blood pressure of 47,XYY and 47,XXY men in a double-blind, double-matched population survey. *American Journal of Human Genetics* 1981 **33** 77–84.

79 Campbell WA & Price WH. Venous thromboembolic disease in Klinefelter's syndrome. *Clinical Genetics* 1981 **19** 275–280. (https://doi.org/10.1111/j.1399-0004.1981.tb00709.x)

80 Zoller B, Ji J, Sundquist J & Sundquist K. High risk of venous thromboembolism in Klinefelter syndrome. *Journal of the American Heart Association* 2016 **5** e003567. (https://doi.org/10.1161/JAHA.116.003567)

81 Corona G, Rastrelli G, Monami M, Guay A, Buvat J, Sforza A, Forti G, Mannucci E & Maggi M. Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study. *European Journal of Endocrinology* 2011 **165** 687–701. (https://doi.org/10.1530/EJE-11-0447)

82 Heinze-Milne S, Banga S & Howlett SE. Low testosterone concentrations and risk of ischaemic cardiovascular disease in ageing: not just a problem for older men. *Lancet. Healthy Longevity* 2022 **3** e83–e84. (https://doi.org/10.1016/S2666-7568(22)00008-3)

83 Gagliano-Jucá T & Basaria S. Testosterone replacement therapy and cardiovascular risk. *Nature Reviews. Cardiology* 2019 **16** 555–574. (https://doi.org/10.1038/s41569-019-0211-4)

84 Chang S, Biltoft D, Skakkebaek A, Fedder J, Bojesen A, Bor MV, Gravholt CH & Munster AB. Testosterone treatment and association with thrombin generation and coagulation inhibition in Klinefelter syndrome: a cross-sectional study. *Thrombosis Research* 2019 **182** 175–181. (https://doi.org/10.1016/j.thromres.2019.08.011)

85 Chang S, Goszczak AJ, Skakkebæk A, Fedder J, Bojesen A, Bor MV, de Maat MPM, Gravholt CH & Münster AB. Reduced fibrin clot lysis in Klinefelter syndrome associated with hypogonadism. *Endocrine Connections* 2022 **11** e210490. (https://doi.org/10.1530/EC-21-0490)

86 Indirli R, Ferrante E, Scalambrino E, Profka E, Clerici M, Lettera T, Serban AL, Vena W, Pizzocaro A, Bonomi M, *et al.* Procoagulant imbalance in Klinefelter syndrome assessed by thrombin generation assay and whole-blood thromboelastometry. *Journal of Clinical Endocrinology and Metabolism* 2021 **106** e1660–e1672. (https://doi.org/10.1210/clinem/dgaa936)

87 Chang S, Larsen OH, Hvas AM, Skakkebaek A, Gravholt CH & Münster AB. Platelet aggregation in Klinefelter syndrome is not aggravated by testosterone replacement therapy: a longitudinal follow-up study. *Andrology* 2023 **11** 456–463. (https://doi.org/10.1111/andr.13330)

88 Bojesen A & Gravholt CH. Morbidity and mortality in Klinefelter syndrome (47,XXY). *Acta Paediatrica* 2011 **100** 807–813. (https://doi.org/10.1111/j.1651-2227.2011.02274.x)

89 Schünemann HJ, Cushman M, Burnett AE, Kahn SR, Beyer-Westendorf J, Spencer FA, Rezende SM, Zakai NA, Bauer KA, Dentali F, *et al.* American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. *Blood Advances* 2018 **2** 3198–3225. (https://doi.org/10.1182/bloodadvances.2018022954)

90 Tartaglia NR, Wilson R, Miller JS, Rafalko J, Cordeiro L, Davis S, Hessl D & Ross J. Autism spectrum disorder in males with sex chromosome aneuploidy: XXY/Klinefelter syndrome, XYY, and XXYY. *Journal of Developmental and Behavioral Pediatrics* 2017 **38** 197–207. (https://doi.org/10.1097/DBP.0000000000000429)

91 Wilson AC, King J & Bishop DVM. Autism and social anxiety in children with sex chromosome trisomies: an observational study. *Wellcome Open Research* 2019 **4** 32. (https://doi.org/10.12688/wellcomeopenres.15095.2)

92 Hasle H, Mellemgaard A, Nielsen J & Hansen J Cancer incidence in men with Klinefelter syndrome. *British Journal of Cancer* 1995 **71** 416–420.

93 Hultborn R, Hanson C, Köpf I, Verbiené I, Warnhammar E & Weimarck A. Prevalence of Klinefelter's syndrome in male breast cancer patients. *Anticancer Research* 1997 **17** 4293–4297.

Received 16 March 2023
Accepted 24 March 2023
Available online 24 March 2023
Version of Record published 26 April 2023