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The epidemiology of sex chromosome abnormalities

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Abstract

Sex chromosome abnormalities (SCAs) are characterized by gain or loss of entire sex chromosomes or parts of sex chromosomes with the best-known syndromes being Turner syndrome, Klinefelter syndrome, 47,XXX syndrome, and 47,XYY syndrome. Since these syndromes were first described more than 60 years ago, several papers have reported on diseases and health related problems, neurocognitive deficits, and social challenges among affected persons. However, the generally increased comorbidity burden with specific comorbidity patterns within and across syndromes as well as early death of affected persons was not recognized until the last couple of decades, where population-based epidemiological studies were undertaken. Moreover, these epidemiological studies provided knowledge of an association between SCAs and a negatively reduced socioeconomic status in terms of education, income, retirement, cohabitation with a partner and parenthood. This review is on the aspects of epidemiology in Turner, Klinefelter, 47,XXX and 47,XYY syndrome.

KEYWORDS

47,XXX syndrome, 47,XYY syndrome, epidemiology, Klinefelter syndrome, Turner syndrome

1 | INTRODUCTION

Sex chromosome abnormalities (SCAs) are the most commonly occurring chromosomal disorders, affecting 1 in 400 newborns (Linden, Bender, & Robinson, 1995). SCAs are characterized by either gain or loss of entire sex chromosomes (aneuploidy), or parts of sex chromosomes (structural abnormalities, e.g., isochromosomes). The best known syndromes among the SCAs are Turner syndrome (45,X), Klinefelter syndrome (47,XXY), 47,XXX syndrome and 47,XYY syndrome.

The current literature on SCA's is dominated by case reports, small single-center cross sectional clinical studies, few clinical experimental studies with in-depth examination of a certain characteristic, for example, neurocognition, endocrinology, fertility, a few longitudinal observational studies typically observing the development of one trait, for example, the development in bone mineralization (Kubler, Schulz, Cordes, Beyer, & Krause, 1992), and finally a few epidemiological studies, all stemming from three countries—United Kingdom, Sweden, and Denmark. Each study design has advantages and drawbacks. Yet, almost all clinical studies of SCAs are characterized by fewer than 100 participants, and many with much fewer participants. This poses obvious problems related to representativeness, internal and external validity, as well as all sorts of bias. For instance, since the vast majority of SCAs are diagnosed during adulthood, most pediatric studies may be marred by ascertainment bias, since patients likely will be skewed toward a more severe phenotype or ascertained according to prenatal diagnosis, although there is no definite proof for this notion. Similar biases extent to clinical studies of adults as well, which in addition can also be troubled by survivor bias.

On the other hand, epidemiological studies will most often include much larger populations, and since the three countries, providing such studies in the area of SCAs, can present nationwide sampling, these studies can also be seen as complete, thus without ascertainment bias. Further, by design, they are also exempt from survivor bias. Epidemiological studies may therefore offer a less biased view of SCAs, although other problems are related to these studies. For example, the choice of control group can introduce problems. In addition, the ever-pervasive problem of non-diagnosis (Berglund et al., 2019; Viuff, Stochholm, Uldbjerg, Nielsen, & Gravholt, 2015) will of course affect epidemiological studies just as any other study. However,

epidemiological studies have many advantages—they can provide rather precise estimates of prevalence, age at diagnosis, morbidity and mortality, and especially focus on the increased co-occurrence of other conditions together with the SCA in question. They can lend information on specific patterns of medication enhancing the information gleaned from data concerning morbidity and mortality (Hagman et al., 2011; Taylor et al., 1967). They can teach us important lessons on socio-economics and thus obliquely inform us concerning the living conditions of individuals with SCAs. Epidemiological studies, however, can usually not teach us concerning clinical data, and, of course, they cannot inform us on the effect of one type of medication versus another like the randomized clinical trial setting. Nevertheless, in settings, where it would be unethical not to give a certain type of medication, like in KS (withholding testosterone for longer periods would be considered unethical) and TS (similar thinking with withholding estradiol), epidemiological studies are probably going to be the best surrogate for randomized clinical trials. This is what we have recently done with the examination of the effect of testosterone supplementation in KS and estradiol supplementation in TS (Chang et al., 2019; Viuff et al., 2020).

This review provides specific insights into the epidemiology of SCAs with the aim to present an up-to-date synopsis of the latest body of knowledge, primarily based on knowledge from epidemiological literature, but includes as well other types of studies such as clinical studies, where relevant. We conclude with perspectives and focus on areas where knowledge is still lacking or is only sparse. The full PubMed database was searched (without time restrictions) in January 2020 by using the keyword "Klinefelter syndrome", "47,XXX syndrome", "47,XYY syndrome" as search term, as well as "epidemiology" and other eponymous variants of the SCAs. Articles relevant to the topic were obtained and reviewed, as well as other papers selected by the authors.

2 | PREVALENCE

Decades ago, primarily in the 1960's and 1970's, a number of newborn cytogenetic surveys were carried out in Scotland, England, Denmark, United States of America, Russia, Japan, and Canada in order to establish the prevalence of babies with chromosome abnormalities surviving to live births, irrespective of whether they normally would have been diagnosed in early infancy. Pooling data from these surveys, with data, including both mosaic and non-mosaic cases as well as cases with TS owing to a structural abnormality of the X-chromosome, an average prevalence of TS, KS, 47,XXX syndrome, and 47,XYY syndrome can be estimated: TS: 50 per 100,000 females (1 per 2,000 females) (24 TS among 48,744 newborn females) (Bochkov, Kuleshov, Chebotarev, Alekhin, & Midian, 1974; Hamerton, Canning, Ray, & Smith, 1975; Jacobs, Melville, Ratcliffe, Keay, & Syme, 1974; Nielsen & Wohlert, 1991), KS: 152 per 100,000 males (1 per 658 males) (84 KS among 55,212 newborn males) (Bochkov et al., 1974; Hamerton et al., 1975; Higurashi, Iijima, Ishikawa, Hoshina, & Watanabe, 1979; Nielsen & Wohlert, 1991; Ratcliffe, 1976; Taylor & Moores, 1967); 47,XXX: 84 per 100,000 females (1 per 1,190 females) (62 47,XXX among 73,990 newborn females) (Goad, Robinson, & Puck, 1976; Hamerton et al., 1975; Maclean, Harnden, Brown, Bond, & Mantle, 1964; Maeda, Ohno, Matsunobu, Yoshihara, & Yabe, 1991; Nielsen & Wohlert, 1991; Ratcliffe, 1976; Robinson & Puck, 1967; Sergovich, Valentine, Chen, Kinch, & Smout, 1969; Taylor & Moores, 1967); and 47,XYY: 98 per 100,000 males (1 per 1,020 males) (51 47,XYY among 52,004 newborn males) (Goad et al., 1976; Hamerton et al., 1975; Maeda et al., 1991; Nielsen & Wohlert, 1991; Ratcliffe, 1976). As these survey studies were conducted within an unbiased population and without any clinical initiative to undertake karyotyping, the average prevalence of SCAs in these surveys may be agreed upon representing the "true" prevalence of SCAs. Thus, in the following, these estimates are referred to as the "expected" prevalence, although it can be speculated whether these estimates are generally applicable to the newborn population nowadays. Since the cytogenetic survey studies were conducted, only few studies, primarily from Sweden, the United Kingdom, and Denmark, have reported on the prevalence of persons diagnosed with SCAs or provided data, which by extrapolation can be used for estimating the prevalence of diagnosed SCAs. Below, for each of the SCAs, these studies will be reviewed. When interpreting the data certain caveats are important to consider. For instance, whether the prevalence reflects the number of diagnosed persons *living* in a population by the end of the study period (total prevalence), the number of persons *ever* diagnosed in a population by the end of the study period (crude prevalence), or whether it reflects the number of diagnosed persons born in a cohort born a given year, irrespective of age at diagnosis? In Denmark, the prevalence of diagnosed SCAs in each birth cohort during 1901–2014 was estimated by combining birth cohort data with national data of the number of persons diagnosed with a SCA during 1960–2014. It showed that the prevalence of diagnosed TS, KS, 47,XXX, and 47,XYY syndrome varied with a characteristic pattern over time; being rather low in the birth cohorts born prior to the 1960's or during the last decades, whereas being considerably higher in the birth cohorts born during the 1960s to the 1990s (Figure 1). The marked increase in prevalence during the 1960s-1990s likely reflects that persons from these birth cohorts have had time to "grow into diagnosis", given that a considerable element of late diagnosis is known to exist. Thus, the average prevalence in these birth cohorts can be considered as representing the "maximum average prevalence" of diagnosed SCAs among newborns in Denmark. Studies reporting on the prevalence of SCAs will be reviewed below. Results are summarized in Table 1.

2.1 | Turner syndrome

In Denmark, by 2014, the maximum average prevalence of persons diagnosed with TS was 59 per 100,000 newborn females (1 per 1,695) (Berglund et al., 2019), thus higher than the expected prevalence of 50 TS per 100,000 females (Figure 1a). Yet the total prevalence was considerably lower as estimated to 35 TS per 100,000 females (1 per 2,847) (980 TS females among a population of 2.84

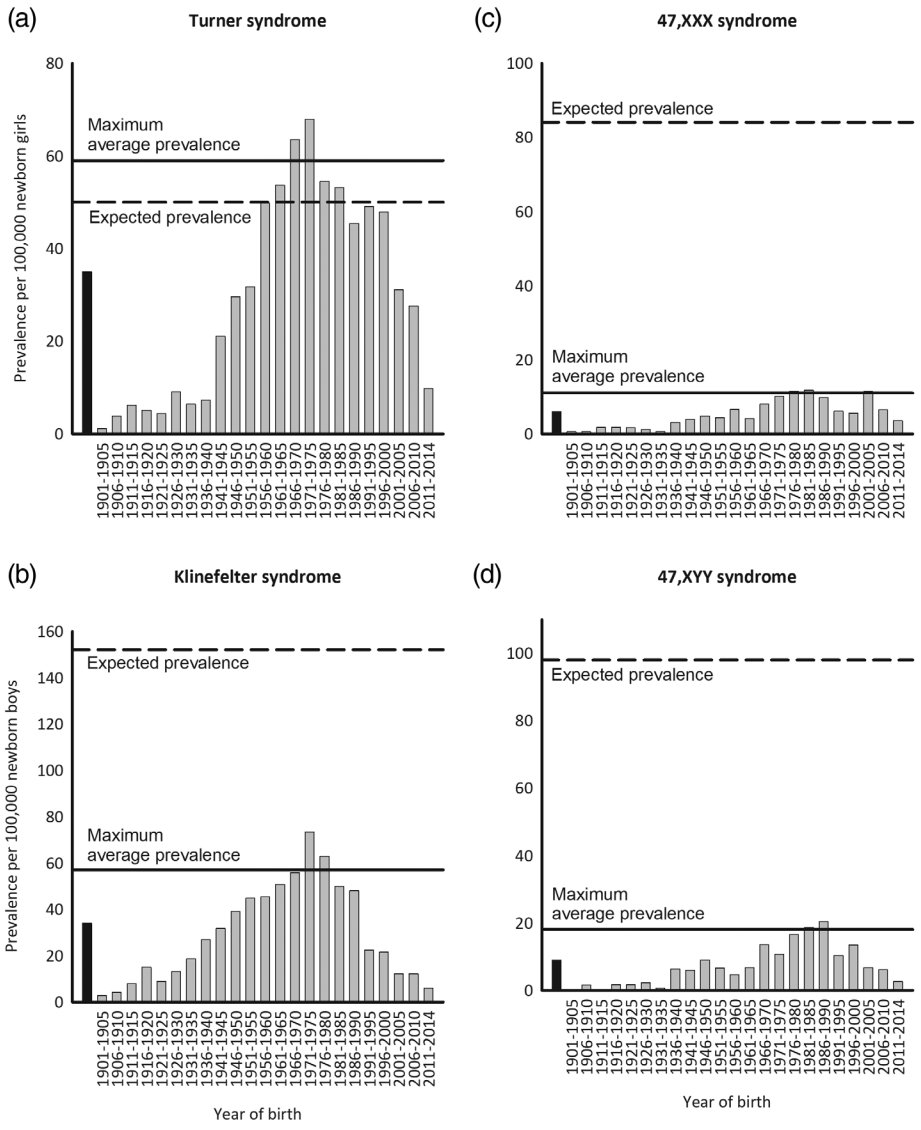

FIGURE 1 Prevalence of diagnosed sex chromosome abnormalities in Denmark. Gray bars indicate the prevalence of diagnosed sex chromosome abnormalities among newborns in Denmark during 1901–2014. Persons were considered prevalent the year they were born. Black bars indicate the prevalence of all diagnosed sex chromosome abnormalities among the total Danish female and male population, all diagnosed persons were living in Denmark by 2014. Solid lines indicate the maximum average prevalence of persons diagnosed with a sex chromosome abnormality (SCA) and dashed lines indicate the expected prevalence estimated from cytogenetic surveys. Revised figure from Berglund et al. (2019)

million females), thus only 70% of expected (Figure 1a). This difference between expected and total prevalence of TS is most likely explained by delayed diagnosis of TS persons, and it demonstrates that a substantial number of TS girls and women in Denmark currently are not diagnosed based on their clinical presentation.

Few other studies provide data for estimation of the TS prevalence. One of these is from Sweden, where Ji et al. identified all persons registered with a diagnosis of TS in either the Swedish Patient Registry or the Swedish Outpatient Registry in order to investigate the risk of solid tumors and hematological malignancy in TS (Ji et al., 2016). By extrapolating data from this study, a crude prevalence of 30 TS per 100,000 females (1 per 3,333) can be estimated (1,409 TS persons among a population of 4.69 million females, 60% of expected). Likewise, extrapolating data from a population-based British study, investigating mortality in TS, 4,909 TS females were identified from 25 out 27 genetic laboratories across the United Kingdom. Among a British female population of 29.45 million females, one can estimate a crude prevalence of 17 TS per 100,000 females (1 per 5,882 females), corresponding to 34% of the expected prevalence (Schoemaker et al., 2008b). Recently, single nucleotide polymorphism (SNP) array data from the UK Biobank were analyzed in order to identify females with X chromosome aneuploidies. Among 240,000 women, aged 40–69 years, and recruited from across the United Kingdom during 2006–2010, the prevalence of women with X chromosome loss was 88 per 100,000 (1 per 1,136 females), thus considerably higher than hitherto reported (176% of expected). This strikingly high prevalence was primarily accounted for by women with 45,X/46,XX mosaicism, which comprised 86% of all identified cases (186 out of 216). The corresponding prevalence of 45,X and 45,X/46,XX was 12 and 76 per 100,000 females, respectively (Tuke et al., 2019).

The UK Biobank study required active participation, and there is evidence of "healthy volunteer" selection bias (Fry et al., 2017). In contrast, TS persons from the other population-based studies in the United Kingdom, Sweden, and Denmark most likely comprise a combination of individuals, with some presenting more overt clinical features as having come to clinical attention, and some that have become diagnosed relatively late in life because of infertility. Consequently, as

TABLE 1 Prevalence of diagnosed sex chromosome abnormalities estimated from population-based studies in Denmark, Sweden, and Great Britain

	Total prevalence	Newborn prevalence
Turner syndrome		
Denmark (Berglund et al., 2019)	35/100,000	59/100,000
Sweden (Ji, Zöller, Sundquist, & Sundquist, 2016)	30/100,000	
Great Britain (Schoemaker, Swerdlow, Higgins, Wright, & Jacobs, 2008b)	17/100,000	
Expected[a]	50/100,000	
Klinefelter syndrome		
Denmark (Berglund et al., 2019)	34/100,000	57/100,000
Sweden (Ji et al., 2016)	23/100,000	
Great Britain (Swerdlow et al., 2005a)	11/100,000	
Expected[a]	152/100,000	
47,XXX syndrome		
Denmark (Berglund et al., 2019)	6/100,000	11/100,000
Great Britain (Swerdlow et al., 2005c)	2/100,000	
Expected[a]	84/100,000	
47,XYY syndrome		
Denmark (Berglund et al., 2019)	9/100,000	18/100,000
Great Britain (Higgins, Swerdlow, Schoemaker, Wright, & Jacobs, 2007)	3/100,000	
Expected[a]	98/100,000	

Note: Total prevalence: prevalence of diagnosed sex chromosome abnormality among all males or females in the population of the given country. Newborn prevalence: maximum average prevalence of diagnosed sex chromosome abnormalities in the Danish birth cohorts.

[a]Based on cytogenetic surveys (Bochkov et al., 1974; Goad et al., 1976; Hamerton et al., 1975; Higurashi et al., 1979; Jacobs et al., 1974; Maclean et al., 1964; Maeda et al., 1991; Nielsen & Wohlert, 1991; Ratcliffe, 1976; Robinson & Puck, 1967; Sergovich et al., 1969; Taylor & Moores, 1967).

the severity of the clinical manifestation of TS is roughly in parallel with the magnitude of deficient X chromosome material (Cameron-Pimblett, La Rosa, King, Davies, & Conway, 2017; El-Mansoury et al., 2007), this likely explains the relatively higher prevalence of women with 45,X/46,XX mosaicism in the UK Biobank study. Still, a prevalence of 76 per 100,000 females (1 per 1,316) is strikingly high. Undoubtedly, women with a 45,X cell line, owing to age-related X chromosome loss, comprise a part of those identified with 45,X/46,XX mosaicism, but since it has been shown that only 0.45% of women aged 75 years have a 45,X cell line (Machiela et al., 2016), the impact on the prevalence is limited.

Most studies on TS show that the proportion of females with 45,X is usually around 40–60%, while the remaining cases are due to 45,X/46,XX (10–20%), karyotypes containing an isochromosome (10–20%), and a combination of other karyotypes (containing a ring chromosome, a Y chromosome, or other variants) (Cameron-Pimblett et al., 2017; Gravholt, Juul, Naeraa, & Hansen, 1998; Zelinska, Shevchenko, & Globa, 2018). This is not trivial, since it is clear that there are at least weak karyotype-phenotype relations, although it has been difficult to clearly delineate these (El-Mansoury et al., 2007). Recent work also indicate rather profound changes in the individual proportions of each karyotype group (Berglund et al., 2019; Tuke et al., 2019), among others due to non-diagnosis, late diagnosis, methodology (the number of cells counted), perhaps early death among the most severely affected and other factors. Therefore, it is important to know the exact karyotype (or even genotype [Murdock et al., 2017]), when comparing different studies and assessing prevalence, morbidity and mortality.

2.2 | Klinefelter syndrome

In a large screening study from Georgia, United States of America, 2009, DNA from dried blood spots from 36,124 newborn boys showed a prevalence of 158 KS per 100,000 newborn males (1 per 632) (Coffee et al., 2009). This is in line with the prevalence of 152 KS per 100,000 newborn males as estimated from the older cytogenetic surveys, as well as with the estimated prenatal prevalence in Denmark of 153 KS per 100,000 males (Bojesen, Juul, & Gravholt, 2003). Still, the prevalence of postnatally diagnosed KS persons is considerably lower. In Denmark, the average maximum prevalence of KS was estimated to 57 per 100,000 newborn males (1 per 1,754) (Berglund et al., 2019), and the total prevalence was estimated to 34 KS per 100,000 males (1 per 2,941) (962 KS among a population of 2.79 million males), corresponding to 23% of the expected prevalence (Berglund et al., 2019) (Figure 1b). Extrapolating data from a population-based British study, identifying males registered with a KS karyotype at 25 out of 27 British genetic laboratories, a crude prevalence of 11 KS per 100,000 (1 per 9,091) can be estimated (332 KS among a population of 29.45 million males), corresponding to 7% of expected (Swerdlow, Schoemaker, Higgins, Wright, & Jacobs, 2005a). Extrapolating data from a Swedish study, in which the authors identified males registered with a diagnosis of KS in either the Swedish Patient Registry or the Swedish Outpatient Registry, a crude prevalence of 23 KS per 100,000 males (1 per 4,347) can be estimated (1,085 KS males among a population of 4.69 million males) corresponding to 15% of expected (Ji et al., 2016). Thus, in Denmark, the United Kingdom and Sweden, more than three-quarters of expected KS males are currently not diagnosed based on their clinical presentation. Interestingly, in a population-based Victorian study (Australia), the prevalence of diagnosed KS males was somewhat higher than in the European studies as estimated to 87 per 100,000 males (1 per 1,149), thus 57% of the expected prevalence. Moreover, among newborns, the study identified a strikingly high prevalence of 223 KS males per 100,000 newborn males (1 per 448) (Herlihy, Halliday, Cock, & McLachlan, 2011). The authors speculate whether Australian women's older age compared to the age of Danish women

when giving birth may contribute to the higher prevalence of KS among Australian newborns. Further, given that the prevalence of KS in an Asian cohort (n = 848) was found to be 355 per 100,000 males (1 per 298), and given that 8% of the Australian populace is being of Asian descent, the authors speculate whether a different racial composition of the Australian populace may affect the prevalence (Herlihy, Halliday, et al., 2011). Though, it is important to emphasize, that there is no evidence to support nor to refute this speculation.

2.3 | 47,XXX syndrome

The total prevalence of girls and women diagnosed with 47,XXX syndrome in Denmark was by 2014 6 per 100,000 females (1 per 16,667) (165 47,XXX females among a population of 2.84 million females), thus only 7% of expected, whereas the maximum average prevalence was 11 per 100,000 newborn girls (1 per 9,091) (Figure 1c) (Berglund et al., 2019). In the United Kingdom, among 25 of 27 genetic laboratories, Swerdlow et al. identified 747 females diagnosed with a karyotype including three or more X chromosomes. Considering a British population of 29.45 million females, a crude prevalence of approximately 2 per 100,000 females (2% of expected) can be estimated (Swerdlow et al., 2005c), thus demonstrating an even lower diagnostic yield than in Denmark. For comparison, among the 240,000 women actively participating in the UK Biobank Study, 110 women with 47,XXX were identified, corresponding to a prevalence of 45 per 100,000 women (1 per 2,222) and 53% of the expected prevalence (Tuke et al., 2019). This very clearly demonstrates that when a clinical initiative to undertake a karyotype is required many females with 47,XXX syndrome escape diagnosis. However, the prevalence of women with a 47,XXX karyotype was still only half of the expected prevalence. There is evidence that UK Biobank participants were less likely to live in socioeconomically deprived areas than non-participants (Fry et al., 2017), and an association between 47,XXX syndrome and lower socioeconomic status has been shown (Stochholm, Juul, & Gravholt, 2013). Combined, this may explain why the observed prevalence is lower than expected.

2.4 | 47,XYY syndrome

In Denmark, by 2014, the total prevalence of males diagnosed with 47,XYY syndrome was 9 per 100,000 males (239 47,XYY males among a population of 2.79 million males, 9% of expected), whereas the maximum average prevalence was 18 47,XYY males per 100,000 newborn males (18% of expected) (Berglund et al., 2019) (Figure 1d). Extrapolating data from a population-based British study of mortality among males diagnosed with two or more Y chromosomes, the diagnostic yield showed to be even lower than in Denmark, as among a population of 29.45 million males, 987 males had been diagnosed with 47,XYY syndrome/polosomy Y. This corresponds to a prevalence of only 3 per 100,000 and 3% of the expected prevalence (Higgins et al., 2007).

3 | AGE AT DIAGNOSIS AND NON-DIAGNOSIS

With a median age at diagnosis of 15.1 (range: 0.0–85.4) years in TS, 27.5 (range: 0.0–82.8) years in KS, 17.9 (range: 0.0–73.2) years in 47,XXX syndrome, and 15.1 (range: 0.0–70.7) years in 47,XYY syndrome (Figure 2), diagnosis of SCAs is considerably delayed (Berglund et al., 2019). In addition, as described above, the diagnostic yield is strikingly low for both KS, 47,XXX, and 47,XYY syndrome, whereas for TS, the diagnostic yield is higher. In Denmark, the maximum average prevalence of diagnosed TS girls and women did indeed correspond to the expected prevalence of TS. Where a well-characterized phenotype is described for TS (short stature, characteristic facial appearance with neck webbing and lymphedema, primary or secondary amenorrhea, and cardiac malformations) (Gravholt et al., 2017), and also a somewhat more precise phenotype in KS (tall stature, small testes, hypergonadotrophic hypogonadism, gynecomastia, and infertility) (Groth, Skakkebaek, Host, Gravholt, & Bojesen, 2013), there is not such a well-established phenotype for 47,XXX and 47,XYY syndrome. Importantly, what is considered the "classic" SCA phenotype may actually present the most extreme manifestation of a SCA. The population of diagnosed SCAs may then fall into three main categories: a rather severe phenotype with a comparatively young age at diagnosis, a milder phenotype with individuals belonging here being diagnosed with a considerable delay (Herlihy et al., 2011), and the phenotype with the prenatally ascertained individuals (Close, Fennoy, Smaldone, & Reame, 2015; Tartaglia, Ayari, Hutaff-Lee, & Boada, 2012). Therefore, we may not know the full clinical spectrum of any of the SCAs, which could disincline many clinicians away from taking the initiative to perform

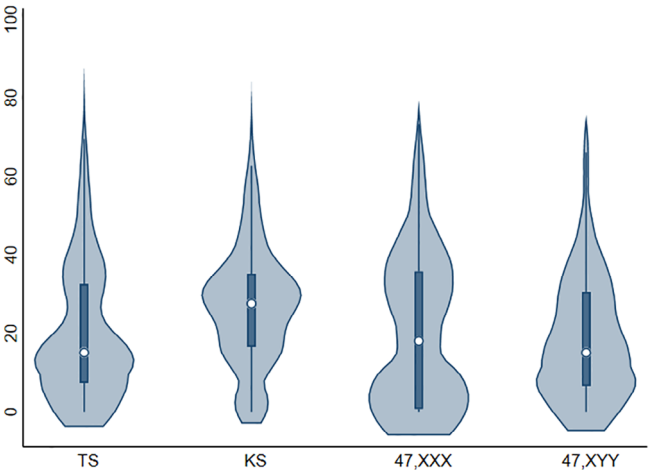

FIGURE 2 Age at diagnosis of sex chromosome abnormalities. Violin plots illustrating age (years) at diagnosis of sex chromosome abnormalities in Denmark during 1970–2014 (47,XXX, 47,XXX syndrome; 47,XYY, 47,XYY syndrome; KS, Klinefelter syndrome; TS, Turner syndrome). The small circle in the middle of the plot is median age, the dark rectangle depicts interquartile range, the thin dark lines depicts 95% confidence interval, and the density plot width equals frequency of age at diagnosis. Revised figure from Bergund et al. (2019)

karyotyping or other measures to diagnose persons with a SCA. It is likely that this is an explanation of why so many individuals affected by KS, 47,XXX and 47,XYY syndrome go through life without being diagnosed. Still, this area needs further investigation. We think that only nationwide neonatal screening programs will show the full phenotypic breath of SCAs.

4 | PRENATAL DIAGNOSIS OF SCAs

Combined first trimester screening based on maternal age, nuchal translucency (NT) thickness, free beta human chorionic gonadotropin (β-hCG), and pregnancy-associated plasma protein-A (PAPP-A) is an effective tool for detection of pregnancies affected by trisomy 13, 18 or 21. However, serendipitous detection of fetuses with SCAs can be considered a side effect of this kind of screening, although risk algorithms are not weighted toward these conditions (Christiansen et al., 2016). In order to assess the ability of the combined first trimester screening to detect SCAs, 134,768 and 140,269 female and male pregnancies in Denmark, which during 2008–2012 had underwent screening, were evaluated. In total, 172 fetuses affected by a SCA were detected, corresponding to a prenatally detected prevalence of 87 TS per 100,000 females (1 per 1,149) (n = 117), 19 KS per 100,000 males (1 per 5,263) (n = 27), 16 47,XXX per 100,000 females (1 per 6,250) (n = 21), and 5 47,XYY per 100,000 males (1 per 20,000) (n = 7) (Viuff et al., 2015). Considering a prenatal prevalence of 209 TS per 100,000 females (1 per 478) (Gravholt, Juul, Naeraa, & Hansen, 1996), 153 KS per 100,000 males (1 per 654) (Bojesen et al., 2003), 84 47,XXX per 100,000 females (1 per 1,190) (Berglund et al., 2019), and 98 47,XYY per 100,000 males (1 per 1,020) (Berglund et al., 2019), this corresponds to 42% of TS fetuses, 12% of KS fetuses, 19% of 47,XXX fetuses, and 5% of 47,XYY fetuses being prenatally detected. Of these, 69% of TS pregnancies (n = 81), 48% of KS pregnancies (n = 13), 24% of 47,XXX pregnancies (n = 5), and 29% of 47,XYY pregnancies (n = 2) ended in termination of the pregnancy (Viuff et al., 2015). These rates of pregnancy termination are somewhat similar to the pregnancy termination rates of KS (≈42%), 47,XXX (≈32%), and 47,XYY (≈28%), which were reported by Boyd et al. after assessment of data collected during 2000–2005 by the European network of registers for the epidemiologic surveillance of congenital anomalies (EUROCAT), which annually surveys more than 1.5 million births across Europe (Boyd, Loane, Garne, Khoshnood, & Dolk, 2011). Further, they were in line with the average termination rates of TS (76%, range: 33–100%) and KS (61%, range: 44–85%), which were reported by Jeon et al. in a review focusing on the decision to abort after a prenatal diagnosis of a SCA (Jeon, Chen, & Goodson, 2012). Applying the pregnancy termination rates observed in Denmark to the expected prevalence of SCAs, one can estimate a decrease in prevalence from 50 to 32 TS per 100,000 newborn females, from 152 to 142 KS per 100,000 newborn males, from 84 to 81 47,XXX per 100,000 newborn females, and from 98 to 97 47,XYY per 100,000 newborn males. Still, it is important to emphasize that the reported rates of pregnancy termination may not be generalizable to all countries. Moreover, with the increasing implementation of multidisciplinary counseling of parents expecting a child prenatally diagnosed with a SCA, pregnancy termination rate may change in the future as more parents may decide to continue the pregnancy. This was the case in a French study investigating the outcomes of 188 KS pregnancies during 1985–2009. After the creation of multidisciplinary prenatal diagnosis centers in 1997, a significant decrease in abortions was observed (46.9–11.6%) (Gruchy et al., 2011). Accordingly, in the review by Jeon et al. it was concluded that if pregnant women received genetic counseling, they were more likely to continue their SCA-affected pregnancy compared with women receiving counseling from non-specialist (Jeon et al., 2012).

Another factor that may impact on the future epidemiologic landscape of SCAs is the increasing implementation of non-invasive prenatal testing (NIPT), as this may affect both the number of SCAs detected prenatally as well as it may affect who is ascertained and how early. In a Victorian (Australia) population-based cohort study from 1986–2016 including all women undergoing prenatal diagnosis before 25 weeks (n = 2,043,345 births) the percentage of NIPT leading to a SCA diagnosis increased significantly from 0.95% in 2010 to 2.93% in 2016. The annual prenatal diagnosis rate of SCAs, however, remained stable at 4.4 per 10,000 births. No data on pregnancy termination rates were provided (Howard-Bath, Poulton, Halliday, & Hui, 2018). No doubt increased use of NIPT in the future may hold the capacity to affect the diagnostic yield of prenatally ascertained SCA's provided that the current problems with sensitivity and specificity are solved.

5 | MORBIDITY

Morbidity among persons diagnosed with a SCA has been described in population-based studies from Denmark, the United Kingdom, and Sweden by investigating national registry data on hospital diagnoses classified according to the seventh, eighth, ninth or 10th edition of the International Classification of Diseases (ICD). Below, morbidity in each syndrome is reviewed separately.

5.1 | Turner syndrome

In a study of all females diagnosed with TS during 1960–1992 (n = 594) and the Danish female population (n = 2,594,036 females), the incidence of diseases suspected to occur with increased frequency in TS were compared using relative risk (RR) as the measure of association (Gravholt et al., 1998). The RR of endocrine diseases, including myxedema, thyroiditis, osteoporosis, and type 1 and 2 diabetes, was substantially increased, likewise was the RR of ischemic heart disease and arteriosclerosis, hypertension, and vascular disease of the brain. Further, liver cirrhosis, and congenital malformations of the heart, of the urinary system, of the face, ears, and neck were significantly increased, whereas no difference in the RR of inflammatory bowel diseases (IBD) was observed. Recently, however, when analyzing the incidence of hospital encounters associated with an IBD diagnosis in

TS females diagnosed during 1960–2014 (*n* = 1,156) and age-matched female controls (*n* = 115,578) from the Danish reference population, the incidence of IBD was significantly increased in TS (incidence rate ratio (IRR) = 3.5 (1.9–6.5) (Viuff et al., submitted data). This supports previous reports on an increased risk of IBD in TS (Price, 1979). For the same cohorts of TS females and reference population controls, there was an increased incidence of hospitals encounters associated with endocrine and cardiovascular disorders as well as with coeliac disease as well (Viuff et al., 2020).

According to TS guidelines, hormone replacement therapy (HRT) should be initiated in TS persons presenting primary or secondary amenorrhea in order to induce puberty, maintain secondary sex characteristics, facilitate uterine growth, ensure appropriate peak bone mass, and improve the metabolic profile (Gravholt et al., 2017). Still empiric data on the long-term consequences of HRT are limited. In order to address the impact of HRT on cardiovascular and endocrine disorders, the incidence of hospital encounters was investigated for 45,X TS females receiving HRT (*n* = 288) in comparison to 45,X TS females not receiving HRT (*n* = 44). Using IRRs as the measure of association, the risk of stroke and hypertension was significantly increased among 45,X TS receiving HRT. Further, HRT was associated with a clear trend toward a reduced risk of type 1 and type 2 diabetes, osteoporotic fractures, and thyroid disorders. In contrast, among TS women receiving HRT, there was an increased risk of ischemic heart disease and hyperlipidemia. Yet the number of events was limited and thus not adding evidence to this issue (Viuff et al., 2020).

All-cause cancer risk in TS has been investigated in population-based studies from the United Kingdom (Schoemaker, Swerdlow, Higgins, Wright, & Jacobs, 2008a), Sweden (Ji et al., 2016), and Denmark (Gravholt et al., 1998), with the British and the Swedish studies reporting standardized incidence rates (SIR) and the Danish study reporting RR estimates. Both the British and the Danish study reported the all-cause cancer risk as being similar to the reference population (Gravholt et al., 1998; Schoemaker et al., 2008a), whereas in the Swedish study, the risk was increased, although only slightly (Ji et al., 2016). Investigating the risk of certain types of cancers in TS, a significant increased risk was found for benign CNS tumors (meningiomas and astrocytomas) and nervous system cancer (Ji et al., 2016; Schoemaker et al., 2008a) as well for gastrointestinal cancer (Gravholt et al., 1998; Hasle et al., 1996). Moreover, in the Swedish study, TS was associated with a three-fold increased risk of melanoma (Ji et al., 2016). Between studies, there is consistency that TS associates with a significantly reduced risk of breast cancer (Ji et al., 2016; Schoemaker et al., 2008a), which likely may reflect a lower-than-average estrogen exposure in these women. Recently, by comparing the incidence of cancer diagnoses among females in the Danish TS cohort diagnosed during 1960–2014 (*n* = 1,156) and age-matched female controls from the Danish reference population (*n* = 115,578 females), TS females showed to have a significantly reduced risk of breast cancer (HR = 0.44, 95% CI: 0.22–0.88), thus substantiating the previous reports hereof. Moreover, TS females did have a two-fold increased risk of skin cancer, excluding melanomas (HR = 2.23, 95% CI: 1.19–4.17) and, interestingly, stratified on karyotype, TS females with a 45,X karyotype had a three-fold increased risk of benign CNS tumors (HR = 3.2, 95% CI: 1.2–8.5) (Viuff et al., submitted data).

At present, the risk of gonadoblastoma among TS with a karyotype including Y-chromosome material is not exactly quantified, but gonadectomy is recommended in these persons (Gravholt et al., 2017). None of the above studies reported an increased risk of gonadoblastoma, clearly highlighting the need of further studies on this topic.

5.2 | Klinefelter syndrome

In order to describe the morbidity pattern in the Danish KS cohort (*n* = 832), the incidence of discharge diagnoses from the Danish National Patient Registry was investigated in comparison to age-matched male controls (*n* = 4,033) from the Danish reference population, yielding HRs as the measure of association. Dividing diagnoses according to the chapters defined in the ICD-10, a significant increased risk for almost all chapters was found, the only exception being for the chapter comprising diagnoses of diseases related to the newborn period (e.g., intra-uterine hypoxia, respiratory distress of the newborn and diseases related to birth trauma). Among endocrine disorders, KS was associated with a significantly increased risk of type 1 and type 2 diabetes, adiposity, myxedema, hypogonadism and osteoporosis (Bojesen, Juul, Birkebaek, & Gravholt, 2006). Infections, anemia, psychiatric disorders (neurocognitive disability, psychoses, disorders of personality/neuroses), neurological diseases (epilepsy and cerebral palsy/paresis), eye disorders, respiratory diseases (pneumonia, asthma, chronic obstructive lung disease), gastrointestinal diseases (intestinal thrombosis, ulcer and liver cirrhosis), diseases of the skin (infections and eczema/bullous disorders), diseases of the musculo-skeletal system (osteoarthritis), urogenital diseases (infections and gynecomastia), congenital malformations (heart and retention of the testes), and disorders owing to a trauma (fractures), were all significantly increased as well (Bojesen et al., 2006). Moreover, KS was associated with a substantial increased risk of cardiovascular disorders, including ischemic heart disease, intestinal thrombosis and cerebrovascular diseases, thrombophlebitis and thrombosis of the veins as well as of pulmonary embolism (Bojesen et al., 2006).

The risk of venous thromboembolism (VTE) was subsequently investigated in a Swedish study, comprising all patients registered with a diagnosis of KS in the Swedish Hospital Discharge Registry and the Swedish Outpatient Registry during 1969–2010 (*n* = 1,085). Using the Swedish male population as reference, KS was associated with a six-fold increased risk of VTE (standardized incidence ratio (SIR), 6.4, CI: 5.2–7.9) (Zoller, Ji, Sundquist, & Sundquist, 2016). The association between KS and VTE was further substantiated in a more recent Danish study, which compared the incidence of VTE diagnoses among KS (*n* = 1,115) with the incidence among reference population controls (*n* = 115,765), yielding a significantly increased HR of 3.9 (CI: 2.8–5.5) (Chang, Christiansen, et al., 2019). In contrast, when investigating diagnoses of arterial thrombotic among the same cohort of KS males and controls, no significant difference was observed. However, KS was associated with a nearly two-fold increased risk of dying from an arterial thrombotic event (HR, 1.7, CI: 1.2–2.5) (Chang, Christiansen, et al., 2019).

Hypogonadism may induce a vicious cycle of abdominal obesity and insulin insensitivity, in turn leading to an increased cardiovascular risk and furthermore skewing of the hemostatic balance (Carrageta, Oliveira, Alves, & Monteiro, 2019; Chang et al., 2019). Testosterone treatment may counteract this vicious cycle and reduce cardiovascular and thrombotic risk, although conversely. It can be speculated that testosterone treatment may increase thrombotic risk by inducing erythrocytosis. In order to investigate the impact of testosterone treatment on the thrombotic risk among men in the Danish KS cohort, those treated with testosterone (n = 563) were compared with those not receiving testosterone (n = 592). This comparison did not show any formal difference in thrombotic risk. Surprisingly, testosterone treated KS men showed to have a significantly increased incidence of prescriptions of antidiabetics, statins, platelet inhibitors, and antihypertensives, suggesting hereby an association between testosterone treatment and an increased cardiovascular comorbidity burden (Chang, Biltoft, et al., 2019). In contrast, one may also speculate whether the increased incidence of these prescriptions indeed indicate a higher standard of care in testosterone treated KS men and missed cardiovascular diagnoses in untreated KS men. For elucidation of this topic, future studies focusing on the long-term effect of testosterone treatment in KS men would be highly appreciated.

The first population-based study investigating cancer risk in KS was based on the cohort of KS men diagnosed in Denmark by December 1992 (n = 696). Information about the incidence of cancer was obtained from the Danish Cancer Registry and then compared with the expected incidence in the Danish male population, yielding a RR. No significant difference in all-cause cancer risk was observed, but the risk of mediastinal germ cell tumors in KS was found to be 67 times increased in the age group from young adolescence to 30 years (Hasle, Mellemgaard, Nielsen, & Hansen, 1995). Subsequently, expanding the KS cohort to 832 KS males, Bojesen et al. compared the incidence of mediastinal tumors among KS males with the incidence among 4,033 age-matched male controls, yielding a HR of 14.2, hereby supporting an association between KS and mediastinal tumors. However, a convincing explanation of such association is lacking. Bojesen et al. did also investigate the incidence of any cancer among KS and controls, yielding a slightly increased HR of 1.3 (CI: 1.03–1.7). Moreover, three cases of breast cancer were observed in the KS cohort, whereas no cases were observed among controls (Bojesen et al., 2006).

In Sweden, all KS males registered in the Swedish Discharge Registry and the Swedish Outpatient Registry during 1969–2010 (n = 1,085) were identified and further linked to the Swedish Cancer Register in order to estimate SIRs of cancer using the general population as reference. Hereby, a significantly increased risk of non-Hodgkin lymphoma, hematological malignancy, and leukemia was found, whereas the risk of solid tumors was significantly reduced. No difference in the overall risk of any cancer was observed (Ji et al., 2016), which is in line with the conclusion of a previous British study, comparing the incidence of cancer among 3,518 KS males diagnosed during 1959–2002 with the expected incidence of any cancer in the British male population (Swerdlow et al., 2005b). The British data, however, showed a significant increased incidence of breast cancer in KS, while the incidence of non-Hodgkin lymphoma and lung cancer was insignificantly increased. Recently, a significantly reduced risk of prostate cancer in KS was identified by Watts et al. (HR, 0.6, CI: 0.37–0.91), when comparing British data on prostate cancer diagnoses among KS (n = 1,992) to a reference cohort of men aged ≥35 years and with no known prior record of prostate cancer. The authors speculate that low circulating testosterone concentrations may reduce prostatic androgen receptor signaling and therefore may reduce prostate cancer risk (Watts et al., 2019).

5.3 | 47,XXX and 47,XYY syndrome

At present, morbidity in 47,XXX and 47,XYY syndrome has not been comprehensively described, and the limited data on morbidity in these syndromes have stemmed only from case reports or small studies. Lately, however, the incidence of diagnoses associated to in- and outpatient hospital encounters during 1977–2014 was investigated in the Danish cohort of males diagnosed with 47,XYY syndrome (n = 251) during 1960–2014, along with an investigation of the incidence of prescribed medication during 1995–2014. For comparison, 25,100 age-matched male controls from the reference population were identified, yielding HRs as the measure of association. By dividing hospital diagnoses according to the chapters defined in the ICD-10, 47,XYY syndrome showed to be associated with a significant increased risk of diseases related to the nervous, respiratory, circulatory, urogenital, and gastrointestinal system, to mental and endocrine disorders, as well as to diseases related to the eye, the skin and the connective tissue and bones. Hospital encounters due to trauma were also significantly increased. Males with 47,XYY syndrome also had an increased risk of several types of medication, including a significant increased risk of having androgens and medication related to the genitourinary system prescribed. Moreover, there was an increased risk of prescriptions related to blood and blood forming organs, the nervous system, the respiratory system, the cardiovascular system, the musculo-skeletal system, and the gastrointestinal system. Systemic hormones, other than sex hormones, dermatologicals, antiinfectives, and medication associated with the sensory organs were more frequently prescribed among 47,XYY males as well (Berglund et al., Genetics in Medicine, article accepted April 2020). These findings strongly suggest that the 47,XYY syndrome is associated with a substantial comorbidity burden, thus having even more far-reaching consequences on long-term health outcome than previously anticipated. Further studies are still needed to support this suggestion.

6 | MORTALITY

Population-based registry studies of mortality in TS, KS, 47,XXX and 47,XYY have been conducted in Denmark and the United Kingdom. In all studies, cause-specific mortality was analyzed by classifying the various causes of death according to chapters in the eighth, ninth, or

10th edition of ICD. Below, results concerning each syndrome are reviewed separately. There is a great need for data from other countries and other continents in order to supplement these data and complete the picture of mortality among persons affected by SCAs.

6.1 | Turner syndrome

In a cohort of 400 TS females identified from three cytogenetic centers in the United Kingdom during 1959–1990, the incidence of mortality was assessed and compared with expectations from British mortality rates among the female population, yielding RR estimates (Swerdlow et al., 2001). This study was later followed-up in an expanded and updated cohort comprising 3,439 TS females diagnosed at 27 out of 29 genetic centers in the United Kingdom during 1959–2002 (Schoemaker et al., 2008b). In both studies, TS was associated with a three- to fourfold increased overall mortality (Table 2), and with a raised mortality for almost all major causes of death including diseases related to the endocrine, nervous, circulatory, respiratory, digestive, genitourinary, and musculoskeletal system as well as due to conditions related to congenital malformations and accidents and violence (Schoemaker et al., 2008b). Circulatory diseases was found to account for 41% of excess mortality, and investigating cardiovascular mortality in more detail, there was a significant increased mortality due to ischemic heart disease, hypertensive disease, aortic valve disease, cerebrovascular disease and aortic aneurysm (Schoemaker et al., 2008b). Previously, among Danish and Swedish TS females, aortic aneurism was estimated to affect 40 per 100,000 TS females compared to 6 per 100,000 in the general population, thus similarly contributing greatly to morbidity and mortality (Gravholt et al., 2006).

Mortality within the Danish TS cohort has been reported in three papers. The first study included all TS females diagnosed during 1970–2000 (n = 741) (Stochholm et al., 2006). This cohort was expanded and followed up in a second (n = 979) and third (n = 1,156) paper (Stochholm, Hjerrild, et al., 2012; Viuff et al., 2020). Where the first study reported on mortality by calculating SMRs bases on mortality rates within the Danish female population, the second and the third calculated HRs by comparing each TS with 100 age-and sex matched controls from the reference population. In all studies, TS was associated with a three-fold increased overall mortality (Table 2), and stratified on karyotype all-cause mortality was most prominent among females with TS due to a 45,X karyotype, which indeed also was reported in the study by Shoemaker et al. (Schoemaker et al., 2008b; Stochholm et al., 2006; Viuff et al., 2020). By comparing 45,X TS receiving HRT with 45,X TS not receiving HRT, a trend toward reduced overall mortality among HRT treated TS was found (Viuff et al., 2020), thus supporting that HRT has a pivotal role in the general health of TS women. The cause-specific mortality associated with TS was reported in both the first and second Danish paper, with the first paper reporting a significantly increased mortality due to endocrine diseases and "other diseases"(accidents, trauma and suicide) (Stochholm et al., 2006). With the second paper, mortality was increased for all ICD-10 chapters, although not necessarily significantly (Stochholm, Hjerrild, et al., 2012).

TABLE 2 All-cause mortality in diagnosed sex chromosome abnormalities

	Risk estimates of all-cause mortality
Turner syndrome	
Swerdlow et al., 2001	4.16 (3.22–5.39)*
Schoemaker et al., 2008b	3.0 (2.7–3.4)**
Stochholm, Juul, Juel, Naeraa, & Højbjerg Gravholt, 2006	2.9 (2.2–3.6)**
Stochholm, Hjerrild, et al., 2012	2.9 (2.4–3.5)***
Viuff et al., 2020	3.3 (2.8–3.8)**
Klinefelter syndrome	
Swerdlow et al., 2001	1.6 (1.4–1.9)*
Bojesen, Juul, Birkebaek, & Gravholt, 2004	1.4 (1.1–1.7)***
Swerdlow et al. 2005a	1.5 (1.4–1.7)**
47,XXX syndrome	
Swerdlow et al., 2001	2.1 (1.4–3.0)*
Swerdlow et al., 2005c	2.5 (1.9–3.2)**
Stochholm, Juul, & Gravholt, 2010b	2.5 (1.6–3.9)***
47,XYY syndrome	
Swerdlow et al., 2001	1.9 (1.20–2.85)*
Higgins et al., 2007	2.0 (1.5–2.6)**
Stochholm, Juul, & Gravholt, 2010a	3.6 (2.6–5.1)***

Note: Risk estimates of all-cause mortality in Turner syndrome, Klinefelter syndrome, 47,XXX syndrome, and 47,XYY syndrome. Risk estimates represents relative risks*, standardized mortality ratios**, or ***hazard ratios. 95% confidence intervals are given in parenthesis. Based on population-based studies from United Kingdom and Denmark (Bojesen et al., 2004; Higgins et al., 2007; Schoemaker et al., 2008b; Stochholm et al., 2006, 2010a, 2010b; Swerdlow et al., 2001, 2005a, 2005c; Viuff et al., 2020).

6.2 | Klinefelter syndrome

All studies have found an increase of mortality among KS males in comparison to controls or the reference population. British data on mortality in 646 males diagnosed with KS during 1959–90 showed that, when compared with expectations from national rates, KS was associated with a 60% increased mortality (RR) (Table 2), most significantly raised from diabetes, non-ischemic heart disease, respiratory diseases, and from vascular insufficiency of the intestine (Swerdlow et al., 2001). This finding was substantiated by a SMR of 1.5 (Table 2) when expanding the cohort to include 3,518 KS males diagnosed during 1959–2003 (Swerdlow et al., 2005a). This study further reported a significantly raised cause-specific mortality from endocrine and metabolic disease (diabetes), mental disorders (primarily alcohol/drug abuse and dementia), and diseases of the nervous (epilepsy), circulatory (pulmonary embolism, cerebrovascular disease, subarachnoid

hemorrhage, other heart disease, and unspecified peripheral vascular disease), respiratory (pneumonia and chronic obstructive airway disease), and genitourinary (renal and ureteric disease) systems as well as from congenital anomalies, primarily being cardiovascular malformations. Mortality due to fracture of femur was increased as well. Mortality due to any cancer was insignificantly increased (Swerdlow et al., 2005a). However, analyses according to cancer site revealed an increased mortality from lung and breast cancers as well as from non-Hodgkin's lymphoma, whereas mortality from prostate cancer was significantly reduced (Swerdlow et al., 2005b).

In Denmark, by comparing the incidence of death in a nationwide cohort of 781 males diagnosed with KS until 1999 with the incidence of death among 3,803 age- and sex matched controls from the Danish reference population, KS was found to be associated with a 40% increased overall mortality (HR = 1.4) (Table 2). Expanding the cohort to include 1,049 KS males diagnosed until 2009, overall mortality was approximately two-fold increased (Table 2), corresponding to a median loss of up to 5.6 life years, and when adjusted for cohabitation and educational status, overall mortality remained significantly increased (HR, 1.5, CI: 1.3–1.8) (Bojesen, Stochholm, Juul, & Gravholt, 2011). The increased mortality was mainly due to infectious (septicemia), neurological, circulatory, respiratory (pneumonia and chronic obstructive airway disease), endocrine and genitourinary diseases (Bojesen et al., 2004; Bojesen et al., 2011). Recently, in an updated analysis comprising all KS males diagnosed until December 2016, mortality under 30 years of age was increased with a HR of 4.2 (2.7 to 6.4), whereas mortality under 15 years of age was increased with a HR of 9.6 (4.4 to 20.8) (Gravholt et al., 2018). Similarly, based on British data, mortality under 45 years of age was associated with a nearly two-fold increased mortality (SMR, 1.8, CI: 1.4–2.2), thus higher than mortality below 65 years of age (SMR, 1.4, CI: 1.2–1.6) (Swerdlow et al., 2005a).

6.3 | 47,XXX syndrome

In the United Kingdom, Swerdlow et al. identified 542 girls and women diagnosed with 47,XXX syndrome (*n* = 513) or polosomy X (48,XXXX, *n* = 18; 48,XXXX/mosaic, *n* = 5, and 49,XXXX, *n* = 6) during 1959–2004 and calculated SMRs using national mortality rates for the female population as reference (Swerdlow et al., 2005c). This study was an expansion of a previous study including 119 cases of 47,XXX syndrome and 2 cases of polosomy X (48,XXXX), in which mortality was analyzed by calculating RR estimates (Swerdlow et al., 2001). These studies revealed an overall mortality that was up to 2.5 times higher than in the general population (Table 2). Similarly, comparing 134 females diagnosed with 47,XXX syndrome in Denmark during 1963–2008 with 13,400 age-matched female controls from the reference population, overall mortality was increased with a HR of 2.5, corresponding to a loss of more than 7 years in median survival (Stochholm et al., 2010b). Including only persons with an age of at least 15 years at the end of the study period, overall mortality was increased with a HR of 2.2 (Table 2), and when adjusted for marital status and cohabitation, the HR was 2.1 (CI, 1.3–3.4) (Stochholm et al., 2013).

In both the United Kingdom and Denmark, cause-specific mortality was increased for diseases associated with the circulatory system (Stochholm et al., 2010b; Swerdlow et al., 2001, 2005c), with the second British study showing an increased risk of mortality due to diseases associated with the circulatory system (ischemic and non-ischemic heart disease) and the respiratory system (pneumonia). Moreover, this study did also identify an increased mortality due to mental diseases, neurological diseases, and congenital anomalies of the cardiovascular system. No difference was observed for mortality due to all-cause cancers, though, mortality due to non-Hodgkin's lymphoma was 10-fold increased (Swerdlow et al., 2005c). In Denmark, none of the cases died due to non-Hodgkins lymphoma (Stochholm et al., 2010b). Thus, this British finding could be a chance observation, or the number of deaths in the Danish cohort is too limited to draw firm conclusions. In addition to the increased mortality due to circulatory system diseases, Danish data showed an increased mortality due to urogenital system diseases, chromosomal disorders/congenital defects as well as due to "unspecified" diseases (Stochholm et al., 2010b).

Suffice to say, relative to the general population, mortality in 47,XXX syndrome is elevated to almost the same level as in TS. This underscores that the 47,XXX syndrome is probably not an innocuous syndrome. However, it is important to stress that these data are of course based on the diagnosed population of females with 47,XXX syndrome, and they cannot as such account for the large proportion remaining undiagnosed. Further, it should be emphasized that the British study comprised females with more than three X-chromosomes. Since these individuals often are more severely affected than those with three X-chromosomes, it is possible that this may have had a negative impact on the study results.

6.4 | 47,XYY syndrome

Until 2008, a total of 208 males had been diagnosed with 47,XYY syndrome in Denmark. Compared to 20,078 sex- and age-matched controls from the reference population, yielding HRs as the measure of association, 47,XYY syndrome was associated with a more than three-times increased overall mortality (Table 2), corresponding to a median loss of 10.4 life years (Stochholm et al., 2010a). When adjusting for marital and educational status, the HR of overall mortality was reduced to 2.7 (CI, 1.9–3.8) (Stochholm, Juul, & Gravholt, 2012). Dividing diagnoses according to ICD-10, cause-specific mortality was increased for all chapters having at least one registration of death for both cases and controls, and mortality was significantly increased for the chapters including cancer, neurological, respiratory, and genitourinary diseases, as well as for the chapters including congenital disorders, unspecified diseases, and trauma (Stochholm et al., 2010a).

In the United Kingdom, mortality among 667 males diagnosed with 47,XYY syndrome (*n* = 659) or other forms of polosomy Y (48,XXYY/mosaic, *n* = 7; unspecified Polosomy Y, *n* = 1) during 1959

to 2005 was compared to mortality rates from the general male population, yielding SMRs as the measure of association (Higgins et al., 2007). Hereby, it was shown that 47,XYY syndrome/Polosomy Y was associated with a two-fold increased overall mortality (Table 2), thus substantiating the increased overall mortality of 1.90 (RR), previously reported by Swerdlow et al. when assessing mortality for a subgroup of this cohort (n = 157) (Swerdlow et al., 2001). For the expanded cohort, cause-specific mortality was reported to be increased due to nervous system diseases (epilepsy), respiratory diseases (pneumonia), circulatory diseases, genitourinary diseases, and congenital anomalies. Mortality due to any cancer was not increased, and no difference in mortality from specific cancer sites was observed (Higgins et al., 2007).

7 | SOCIOECONOMIC STATUS

The increased morbidity and mortality affecting individuals with TS, KS, 47,XXX and 47,XXY syndrome demonstrate the profound effect that SCAs may have on long-term health outcome. The pattern of both morbidity and mortality is, however, very diverse and can be difficult to reconcile to the phenotypic characteristics typically presented by individuals diagnosed with a SCA. Underlying genetic mechanisms and hypogonadism may explain part of the patterns observed, whereas differences in socioeconomic status may explain other parts. In order to describe the socioeconomic status of individuals affected by SCAs, nationwide Danish registry data upon cohabitation status, parenthood, educational achievement, income, and retirement from the labor market were investigated for the national cohorts of TS (n = 831), KS (n = 1,049), 47,XXX (n = 108), and 47,XYY syndrome (n = 206), in comparison to age- and sex-matched controls from the Danish reference population (Bojesen et al., 2011; Stochholm et al., 2013; Stochholm, Hjerrild, et al., 2012; Stochholm, Juul, & Gravholt, 2012). Income was analyzed annually by conditional logistic regression, yielding an odds ratio (OR) as the measure of association. All other outcomes were analyzed by Cox regression, including only the *first* registration of an event, even though some variables may have had multiple registrations. If relevant, analyses were divided on the time at risk *before* the SCA diagnosis and on the time at risk *after* the SCA diagnosis in order to account for an eventual impact of the diagnosis on the outcomes studied. Results are summarized in Table 3.

The incidence of cohabiting with a partner was significantly reduced for both TS, KS, 47,XXX, and 47,XYY syndrome with HRs ranging from 0.45 to 0.68. In general, HRs were lower *before* the SCA diagnosis than *after* the SCA diagnosis, suggesting a negative association between one becoming aware of the SCA diagnosis and the impetus to initiate cohabitation (Bojesen et al., 2011; Stochholm et al., 2013; Stochholm, Hjerrild, et al., 2012; Stochholm, Juul, & Gravholt, 2012). It is therefore likely, that awareness of the SCA to some degree influences a person's expectations and self-esteem or that potential partners view the diagnosis as an impediment for a viable relationship. Diminished social abilities (Gotz, Johnstone, & Ratcliffe, 1999; Leggett, Jacobs, Nation, Scerif, & Bishop, 2010; McCauley, Ito, & Kay, 1986; van Rijn, Swaab, Aleman, & Kahn, 2008) might impact negatively on the chances of finding a partner as well.

Infertility is a major concern in both TS and KS, and the proportion of women with TS giving birth was found to be significantly lower than among controls (Stochholm, Hjerrild, et al., 2012). The proportion of KS men registered as fathers were significantly reduced as well (Table 3) (Bojesen et al., 2011). None of the studies accounted for the mode of achieving pregnancy. In Sweden, among 112 women who were diagnosed with TS during 1973–2007 *and* were giving birth, 45% (n = 50) were reported with a 45,X/46,XX karyotype (Hagman et al., 2011). This is somewhat similar to findings from Denmark, where 43% (77 out of 181) of TS women giving birth were reported to have a 45,X/46,XX karyotype (Stochholm, Hjerrild, et al., 2012). Among females and males diagnosed with 47,XXX and 47,XYY syndrome, respectively, the incidence of parenthood was significantly reduced as well (Table 3) (Bojesen et al., 2011; Stochholm, Juul, & Gravholt, 2012), thus, for 47,XYY syndrome, in line with the recent finding of an increased incidence of hospital encounters (including both in- and outpatient encounters) associated with a diagnosis of infertility (IRR; 11.-3, CI: 6.0–21.2) (Berglund et al., Genetics in Medicine, data accepted April 2020). Infertility may therefore be a very likely contributing factor to the reduced incidence of parenthood in 47,XYY syndrome.

Educational achievement was analyzed by defining education as a Bachelor's degree. Among KS, 47,XXX and 47,XYY syndrome, the incidence of achieving an education was substantially reduced with HRs of approximately 0.30 (Bojesen et al., 2011; Stochholm et al., 2013; Stochholm, Juul, & Gravholt, 2012) (Table 3). Both KS and 47,XYY syndrome, the incidence was more prominently reduced after the SCA diagnosis than before the SCA diagnosis (HR_{KS}: 0.40 vs. 0.18,

TABLE 3 Socioeconomic status in persons diagnosed with a sex chromosome abnormality

	Turner syndrome	Klinefelter syndrome	47,XXX syndrome	47,XYY syndrome
Cohabitation	0.45 (0.40–0.50)	0.66 (0.59–0.72)	0.68 (0.49–0.95)	0.50 (0.37–0.66)
Children	0.18 (0.16–0.21)	0.24 (0.21–0.27)	0.64 (0.48–0.85)	0.35 (0.26–0.46)
Education	1.00 (0.87–1.15)	0.27 (0.20–0.37)	0.36 (0.18–0.73)	0.35 (0.18–0.71)
Retirement	1.8 (1.5–2.2)	2.4 (2.1–2.4)	1.9 (1.3–3.0)	4.2 (3.0–5.8)

Note: Hazard ratios of the incidence of cohabitating with a partner for the first time, having a child for the first time, achieving an education, and retiring from the labor market compared to age- and sex-matched controls. 95% confidence intervals are given in parenthesis (Bojesen et al., 2011; Stochholm et al., 2013; Stochholm, Hjerrild, et al., 2012; Stochholm, Juul, & Gravholt, 2012).

$HR_{47,XYY}$:0.59 vs. 0.29). In contrast, there was no difference in the incidence of achieving an education comparing TS women and controls (Table 3), or when dividing the analyses on the time before and after the TS diagnosis. However, after diagnosis, TS women had a two-fold increased risk of retiring from the labor market (HR, 2.0, CI: 1.7–2.4), whereas before diagnosis, no significant difference was observed (Stochholm, Hjerrild, et al., 2012). The overall incidence of retirement was significantly increased in KS, 47,XXX, and 47,XYY syndrome as well (Table 3), and in both KS and 47,XYY syndrome, the incidence was more prominently increased after diagnosis than before diagnosis (Bojesen et al., 2011; Stochholm et al., 2013; Stochholm, Juul, & Gravholt, 2012). This difference may be due to easier acceptance of an application for retirement, when a syndrome has been diagnosed. Based on these findings, one could therefore speculate that diagnosis of a SCA may lead to poorer socioeconomic performance, and that late diagnosis per se would lead to a better performance. Still, data cannot prove such causality.

Income was analyzed by excluding all persons from the year of retirement and onwards. Among men with KS and 47,XYY syndrome annual income was greatly reduced through life compared to controls. Including only persons without an education, this pattern did not change, thus indicating marginalization of KS and 47,XYY men on the labor market (Bojesen et al., 2011; Stochholm, Juul, & Gravholt, 2012). A different pattern was observed among TS and 47,XXX women, as annual income was reduced before the age of 30, whereas no difference was observed hereafter (Stochholm et al., 2013; Stochholm, Hjerrild, et al., 2012).

8 | CONSIDERATIONS AND PERSPECTIVES

Although one could say that the prevalence of SCA's was determined many years ago with large chromosome survey studies in different countries, it is clear from recent epidemiological studies that many, if not most, individuals with SCA's are diagnosed late (perhaps too late?) or never. Many with SCA's are thus not receiving the optimal medical care and attention in for example, the education system, what perhaps could be pivotal to achieving an education and hereby improving the socio-economic status. Albeit differences in size and design, the reviewed studies concerning morbidity and mortality are uniform and clearly show that persons being born with a SCA experience an increased comorbidity burden and earlier demise compared with the general population. Moreover, from studies of the Danish SCA cohorts, it is obvious that a SCA may have even more far-reaching consequences as, overall, among persons diagnosed with a SCA we found a negatively reduced socioeconomic status compared to the general population. Thus, the daily life lived by SCA persons are adversely affected on a wide range of parameters. Epidemiological studies do not allow us to conclude on the underlying mechanisms leading to the increased morbidity, mortality, or late diagnosis observed in SCA persons. Where complex genetic mechanisms may have a direct effect on some of the diseases observed with increased frequency, hormonal imbalances due to gonadal dysfunction may have a direct or indirect effect on the development of other diseases. It also seems clear from the reviewed literature that a sizable proportion of at least individuals with TS and KS are not receiving appropriate hormonal substitution treatment. Moreover, many of the diagnoses observed with increased frequency among SCA persons may be caused by an unfavorable lifestyle associated with a reduced socioeconomic status.

Future studies around the world, and especially outside of Northern Europe, should focus on establishing similar epidemiological data to consolidate further the knowledge base. Several questions deserves special attention. For example, how detrimental is late diagnosis to the life of SCA persons? Would early diagnosis in combination with a multidisciplinary clinical approach improve long-term health outcome in SCA persons? Can intervention from early childhood improve school performance and social abilities and thus in turn improve socioeconomic status in adult life? Which kind of intervention would moreover be the best? What about the large proportion of SCA persons escaping diagnosis? Do they differ from those coming to clinical attention and how? One could argue that those not being diagnosed are similar to the general population and then why bother to identify them? From daily clinical practice, we have the impression that even being diagnosed very late in life, SCA persons recount about a life with many problems often including a problematic time at school with bullying, a feeling of "being different" during puberty and onwards, and often they struggle to keep up in the educational system and on the labor market. Therefore, we advocate for early diagnosis of SCA persons with the incorporation of diagnostics of SCAs into neonatal screening programs. Epidemiology can help in posing relevant clinical questions, which some cases also can help in providing answers, for example, questions concerning hormonal substitution in TS and KS, where large randomized clinical trials probably never will be performed.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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