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Poor socio-economic status in 47,XXX – an unexpected effect of an extra X chromosome

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Running title: Socio-economic status in 47,XXX

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Abstract

One of the most common sex chromosomal abnormalities in females is 47,XXX syndrome, which is characterized by tall stature and reduced IQ, but with a variable phenotype. In order to elaborate on the characteristics of this syndrome, we undertook an investigation in all diagnosed 47,XXX females at risk in Denmark and compared their socio-economic status with an age-matched cohort of the female background population as well as with all Danes diagnosed with Turner syndrome. We focused on cohabitation, motherhoods, income, education, retirement and convictions. Furthermore, we investigated whether some of these parameters influenced the increased mortality identified previously. Thus, socio-economic data were retrieved in 108 47,XXX persons, 10,297 controls, and 831 with Turner syndrome. Comparing the 47,XXX persons with their controls, we identified significantly decreased numbers of first partnership, number of mothers, and number of persons with an education in 47,XXX persons. Significantly more 47,XXX persons retired. In the younger age groups an increased number had income below the median among controls. The increased mortality identified previously was not explained by the reduced number of partnerships or the reduced number of persons with an education. Comparing the 47,XXX persons with Turner syndrome persons, we identified increased number of first partnership, number of mothers, and reduced level of education. We hypothesize that the significantly decreased number of 47,XXX persons becoming mothers could be due to hypogonadism in some. The affected socio-economic status suggests that the presence of an extra X chromosome has more detrimental effects than previously appreciated.

Key words

47,XXX, Turner syndrome, socioeconomic status, mortality, retirement, fertility

ACCEPTED MANUSCRIPT

Introduction

47,XXX women are characterized by tall stature, reduced IQ compared to controls and with motor deficits [1]. However, their clinical phenotype is ambiguous and not necessarily abnormal [2,3] according to small studies with inherent ascertainment bias.

Verbal and academic difficulties are well recognized in 47,XXX girls diagnosed in screening programs [2,4,5]. Information regarding morbidity in general is scarce, whereas the significantly increased mortality identified in 47,XXX women is yet unexplained [6,7]. Whether a linkage exist between the poorer performance and the increased mortality in 47,XXX persons is still unknown [6]. The genetic background for the phenotypic consequences of 47,XXX are not resolved and it is only known that the increased expression of the SHOX gene [8,9] affects height, which is increased in 47,XXX [10]. We have recently documented that the socio-economic status of persons with other sex chromosome abnormalities is impaired and to a varying degree affect mortality. Females with Turner syndrome achieve a high educational level and earn salaries which are comparable to matched healthy females, but have few children, retire early and cohabitate more rarely [11], but this differentially affected status does not materially affect mortality. On the contrary, the socio-economic status of males with both Klinefelter syndrome and 47,XYY syndrome is poorer in comparison with a matched male control population and affects mortality detrimentally [12,13].

In order to investigate the socio-economic status of females with 47,XXX and the association with mortality we compared all diagnosed Danish 47,XXX persons at risk with an age-matched female background population, as well as with all diagnosed with Turner syndrome. We anticipated that females with 47,XXX would have a similarly affected profile as females with Turner syndrome and that mortality would also be affected. We focused on partnership, income, education, retirement, motherhood, and convictions. We analyzed mortality without and with adjustment for partnership and education.

Material

Using the Danish Cytogenetic Central Registry (DCCR), we identified all Danes diagnosed with 47,XXX or a related karyotype. Basic epidemiological findings in these persons have been described previously [6]. Only 47,XXX persons being more than 15 years of age at the end of the study period were included in the following analyses. DCCR contains all information regarding cytogenetic analyzes undertaken nationwide since 1960, including date of diagnosis. Identification numbers (ID-numbers) enable identification of every single person, who is tested with an aberrant chromosomal analysis. ID-numbers were given to all Danish citizens in 1968 and onwards. For each 47,XXX syndrome person, Statistics Denmark identified 100 age and calendar-time matched controls (matched on month and year of birth) from the female background population. All controls were alive and living in Denmark on the date their 47,XXX person was diagnosed.

As another control group we used a cohort of women diagnosed with Turner syndrome in Denmark (n=831). All were more than 15 years of age at the end of the study period.

None of the registries contain information regarding phenotype or the indication for performing the chromosomal analyzes, or information regarding quality of life, intelligence, and lifestyle, for instance smoking, physical activity, or diet.

Methods

Statistics Denmark

From Statistics Denmark we retrieved registration of socio-economic parameters on cohabiting partnerships, number of births, income, education, retirement, convictions, and vital status. The

definitions regarding these social parameters have been described previously, for details see [11]. The registrations of the socio-parameters were primarily from 1984 to 2006, however this period varied.

In brief, most parameters were given annually and we focused on incident events, as the first change from single to not-single, birth of first child, from not retired to retired and first conviction. The achievement of a bachelor degree was considered “an education”. With regards to income, see the Statistics section.

Statistics

For the various socio-economic parameters, median age at first relevant episode was calculated, and we used the Kruskal-Wallis test to compare age distributions.

Kaplan-Meier estimates were constructed for first event of partnership, motherhood, education, retirement, and conviction. The overall time at risk started at the relevant entry age (e.g., 15 years) and ended at the date of first event or at the relevant exit age (e.g., 50 years), whichever came first. Time at risk before diagnosis ended no later than the date of diagnosis, and time at risk after diagnosis started no earlier than the date of diagnosis.

Hazard ratios (HR) and p-values were calculated using Cox regression where each 47,XXX syndrome person and her matched controls were a stratum, hereby adjusting for age and calendar time.

Income was analyzed annually using conditional logistic regression, where each case and her matched controls were one stratum. As retired persons are supported with a fixed and reduced income, they were excluded from analyses of income, from the first registration of retirement and onwards. Data are presented in five-year intervals. The dependent variable was dichotomous, indicating whether the income was above or below the median income among controls in the five-year interval. The standard error reported is a robust standard error estimate.

As we could not ensure age- and calendar-time-matching between 47,XXX and the control group consisting of Turner syndrome, we had year of birth as a covariate in all these comparisons.

We only used the primary cause of death. We translated all ICD-8 diagnoses to ICD-10, and categorized the deaths into the nineteen chapters corresponding to ICD-10 for analyses of cause-specific mortality. HRs were calculated for all chapters, as well for all-cause mortality. Mortality in 47,XXX persons compared to controls was analyzed adjusted for partnership and education.

All results are shown with 95% CI, or with range if relevant, and $p < 0.05$ was considered statistically significant. We made no formal correction for multiple comparisons. We used Stata 11.2 (Stata Corp. College Station, TX, USA) for all calculations.

Results

A total of 134 women with 47,XXX syndrome were identified, of whom 108 were at least 15 years old before the end of the study period and thus included in the following analyses. They were divided into two subgroups according to karyotype, one with "pure" 47,XXX persons (n=62) and one including mosaics (46,XX/47,XXX) (n=46). Statistics Denmark identified 10,297 controls, matched on gender and age. At least 81 controls were identified for each index-person. The main findings are shown in Table 1.

47,XXX versus controls

For 47,XXX persons the over-all incidence of entering a first cohabiting partnership was significantly decreased (Fig. 1). By the age of 30 years 88 percent of the controls alive had been in a cohabiting partnership at least once, whereas the corresponding percentage in 47,XXX persons was 79%. Before the diagnosis the hazard ratio (HR) was 0.99 (95% CI: 0.61-1.61), and after the diagnosis the HR was 0.52 (95% CI: 0.33-0.83).

The HR of 47,XXX women giving birth at least once was significantly decreased (Fig. 2). Sixty-three percent of the controls had given birth by the age of 30 years, corresponding to 50 percent in 47,XXX persons. The HR in the subgroup of 46,XX/47,XXX was 0.73 (95% CI: 0.50-1.06, p=0.10).

The odds ratio (OR) of income above the median was significantly decreased in the younger age groups (Fig. 3). The overall OR of achieving an education was 0.36 (95% CI: 0.18-0.73).

The HR of retiring was significantly increased (Fig. 4). By the age of thirty years 11.7% of the 47,XXX persons and 1.1% of the controls were retired. The HR before the diagnosis was 5.4 (95% CI: 2.2-13.3) and 1.18 (95% CI: 0.72-1.94) after the diagnosis. The number of 47,XXX person ever convicted was similar to controls (OR: 1.05 (95% CI: 0.62-1.78)) (Table 1).

We have previously identified an all-cause mortality in all diagnosed 47,XXX persons in Denmark, only adjusted for age and calendar time, with a HR of 2.5 (95% CI: 1.6-3.9) [6]. In this population, where only 47,XXX persons at least 15 years of age at the end of the study period, are included, the all-cause mortality HR is 2.2 (95% CI: 1.4-3.6). Adjusted for partnership and educational status the ratio was 2.1 (95% CI: 1.3-3.4). Fig. 5 shows all-cause and cause-specific mortality ratios adjusted for these social data.

47,XXX versus Turner syndrome

The 47,XXX women were diagnosed at a significantly older age than Turner syndrome women (median age at diagnosis 26.7 vs. 17.5 years). 47,XXX had an increased number of first partnership (HR: 1.20 (95% CI: 1.01-1.43), $p < 0.05$), were more likely to become mothers (HR: 9.8 (95% CI: 6.4-15.1, $p < 0.001$), but had a reduced level of education (HR: 0.62 (95% CI: 0.43-0.88), and a reduced income (OR: 0.95 (95%CI: 0.89-1.00, $p = 0.06$), although the latter did not reach significance. There were no significant differences regarding retirement (results not shown). 47,XXX women had a similar number of first convictions (HR: 1.21 (95% CI: 0.917-1.60) compared to Turner syndrome. Mortality in 47,XXX women was similar, with no change when further adjusted for partnership and education (no data shown).

Discussion

This study shows important differences between women diagnosed with 47,XXX syndrome and an age-matched female population as well as a group of persons with Turner syndrome, concerning cohabitation, giving birth, income, education, retirement, and mortality.

The significantly decreased chance of cohabitating and of becoming mothers among 47,XXX females compared to controls is a novel finding and not readily explained. However, a combination of decreased self-confidence, and increased shyness, and sensitiveness in 47,XXX persons [1] can possibly explain an impaired drive and opportunity to be intimate with another person. Our data do not provide any answers as to the cause of the reduced number of first partnership or the reduced number of mothers, however we consider the association to women diagnosed with 47,XXX important. Undoubtedly, fertility is preserved in some 47,XXX persons, with pregnancies and childbirth described in many papers, one of the first from Barr et al [14]. However, it may not be a coincidence that the first woman reported with the syndrome, was hypogonadal and had secondary amenorrhea [15]. Our findings suggest a near normal fertility until approximately 25 years of age. Hereafter the advent of premature ovarian failure (POF) might also augment the gap between 47,XXX and controls. POF has previously been described in 47,XXX persons [16]. However, more data on sex hormone status in 47,XXX are dearly needed. As long as data on sex hormone status are not available, we suggest that clinical care of 47,XXX persons also should include annual routine sex hormonal status in teenage girls and onwards and that ultrasound examination of the genitourinary region should be undertaken at least once in the young adult.

The reduced IQ identified in various cohorts of 47,XXX persons compared to controls [2,17,18] combined with the phenotype characterized previously may explain the increased OR of retirement and the reduced income and educational level in 47,XXX persons, where age seemed to influence income. To which degree 47,XXX is associated with autism and neurodevelopmental problems is still being investigated. Previously, in a case report of two persons with 47,XXX, autism spectrum disorders

and requirement of intensive support in activity centers were described [19]. However, in a group of 58 girls with 47,XXX, Bishop et al. found educational difficulties, but none diagnosed with autism spectrum disorders [20]. One of the major problems when investigating these matters is the selection bias present in most cohorts, including ours.

We speculated that an extra sex chromosome would increase the risk of criminality, but found no association between 47,XXX syndrome and convictions; an important finding as the lower IQ, the reduced educational level, and the more vulnerable personality in the 47,XXX person could have resulted in more violations of the law. We found it interesting to study the number of convictions due to our recent confirmation of old data that males with Klinefelter syndrome and 47,XYY have increased rate of criminality compared to the background population [12]. This increased criminality is unexplained, but these new data seem to suggest that it is not merely an effect of the extra sex chromosome.

All-cause mortality did not change after further adjustment for partnership and education. Thus we can probably consider the increased mortality to be directly related to the syndrome, and not an indirect effect of the poorer socio-economic status. It remains to be determined whether females with 47,XXX also show an increased morbidity in comparison with a control population.

The drawbacks of this study are the lack of clinical data and of the reasons for performing the karyotyping. Hereby, the results presented cannot be linked to a specific phenotype within the 47,XXX persons. Furthermore as all data are from diagnosed 47,XXX persons, extrapolation to undiagnosed 47,XXX as a cohort is not advisable. The literature on 47,XXX persons are primarily based on the impressive screening studies which began in the early 1970s, where many of the children identified were followed longitudinally. Moreover, much information originates from case reports, where the triple X syndrome often is associated with congenital abnormalities or other difficulties, introducing selection bias. Here we present data on large cohort of 47,XXX persons, defined by being diagnosed primarily due to clinical suspicion of a possible syndrome. These 47,XXX persons therefore represent the patients that come to the

attention of clinicians and are seen in their daily clinics. Nevertheless, it is important to be aware of possible differences in 47,XXX persons identified in screening studies, as a part of prenatal screening [21], and the ones identified in the daily clinic. We recommend that information presented here regarding the characteristics of 47,XXX persons can lead to a wider diagnostic awareness, and to improvement in the follow-up of these persons.

Conclusion

In a nationwide cohort of all diagnosed 47,XXX persons, older than 15 years of age, we have identified a significantly decreased income, number of first cohabiting partnership, number of mothers, educational level, and a significantly increased number of early retirements compared to an age-matched female background population. The different socio-economic profile did not explain the significantly increased mortality in 47,XXX syndrome identified previously. Compared to Turner syndrome persons, 47,XXX persons were more likely to have a partnership and become mothers, whereas their educational level and income was impaired.

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Figure 1

Proportion of 47,XXX syndrome persons with partner

Kaplan-Meier plot demonstrating the proportion of 47,XXX syndrome persons (bold line) and their controls (bold dashed line) registered with a cohabiting partner for the first time. For comparison we have included similar data for females with Turner syndrome (TS)(thin line). We have omitted the survival graph for the controls for the Turner syndrome females for clarity, which was virtually identical to the survival graph for the 47,XXX controls [1]. HR: Hazard ratio.

Figure 2

Proportion of 47,XXX syndrome persons with a child

Kaplan-Meier plot of proportion of persons with a registration of firstborn child in 47,XXX syndrome persons (bold line) and controls (bold dashed line). For comparison we have included similar data for females with Turner syndrome (TS) (thin line). We have omitted the survival graph for the controls for the Turner syndrome females for clarity, which was virtually identical to the survival graph for the 47,XXX controls [1]. HR: Hazard ratio.

Figure 3

Income above median for 47,XXX syndrome persons

Odds ratios of income above the median for 47,XXX persons vs. controls. Per 5 year intervals of age, the median income was identified for each case's controls. The ratios are adjusted for calendar year. All retired persons are excluded from being at risk from first year of registration of retirement. Vertical lines indicate 95% confidence intervals.

Figure 4

Proportion of 47,XXX syndrome persons who retired

The proportion of 47,XXX syndrome persons (bold line) and controls (bold dashed line) with a first registration of retirement (for details see materials and methods). For comparison we have included similar data for females with Turner syndrome (TS) (thin line). We have omitted the survival graph for the controls for the Turner syndrome females for clarity, which was virtually identical to the survival graph for the 47,XXX controls [1]. HR: Hazard ratio.

Figure 5

Mortality in 47,XXX syndrome persons

All-cause and cause specific HRs of mortality in 47,XXX syndrome persons compared to controls (o), and mortality ratios adjusted for marital status and education (•). Numbers in parentheses indicate number of deceased persons, 47,XXX syndrome persons and controls, respectively. Only informative chapters are included. Note log-scale on the X-axis.

Proportion
who ever had a partner

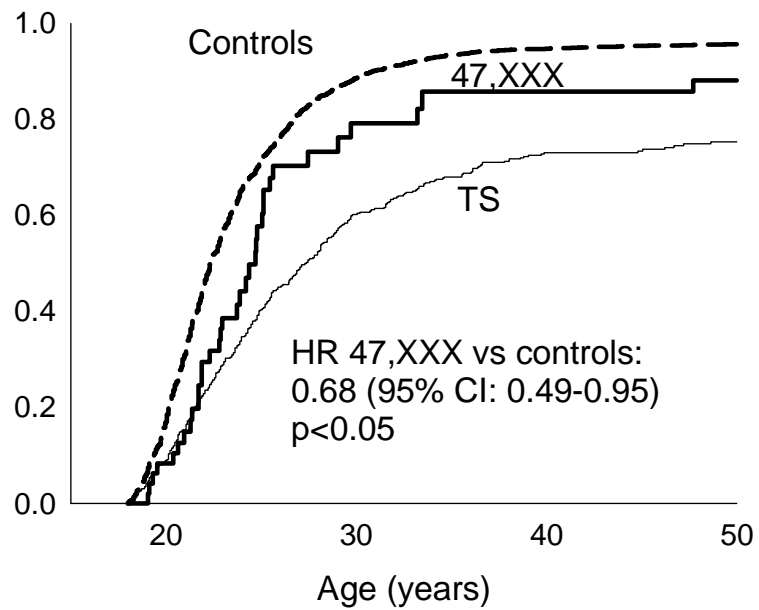


Figure 1

Proportion
giving birth

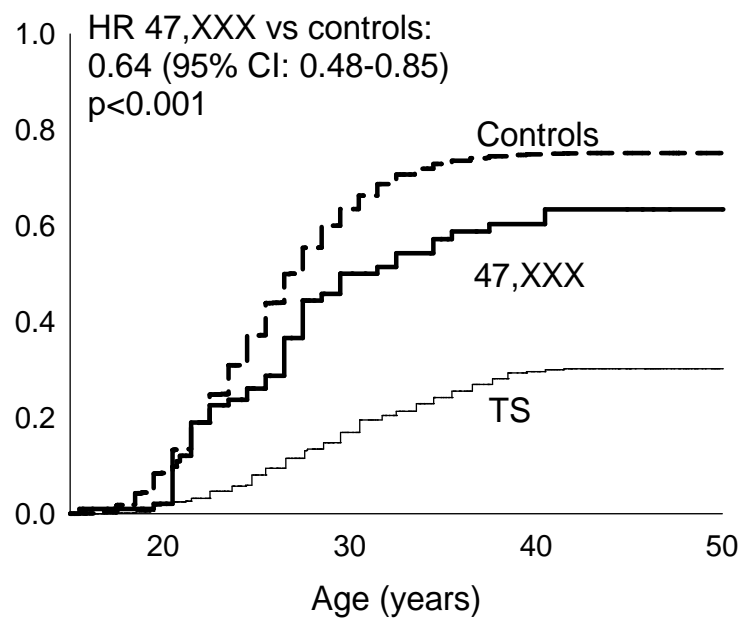


Figure 2

Odds ratio. Log scale
Income above median
47,XXX vs. controls

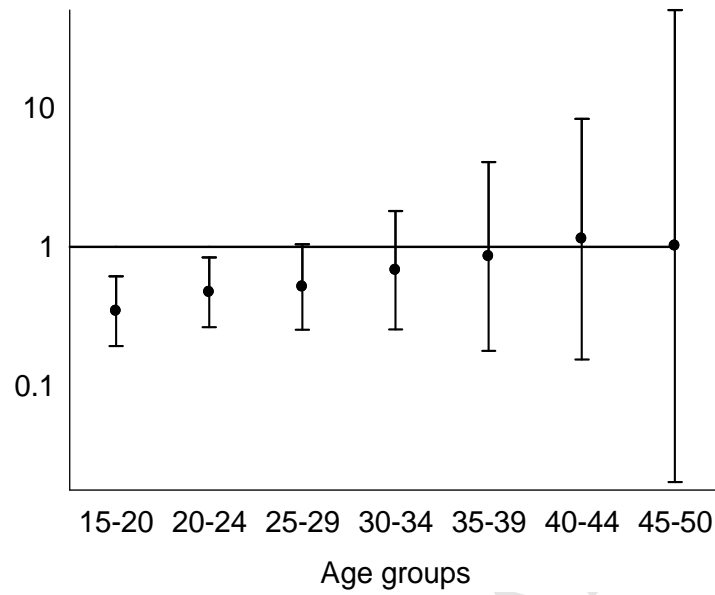


Figure 3

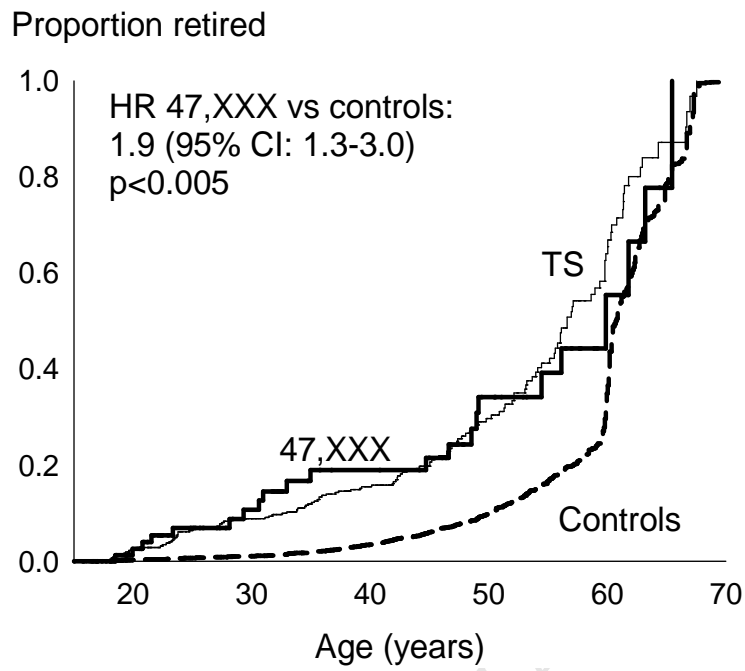


Figure 4

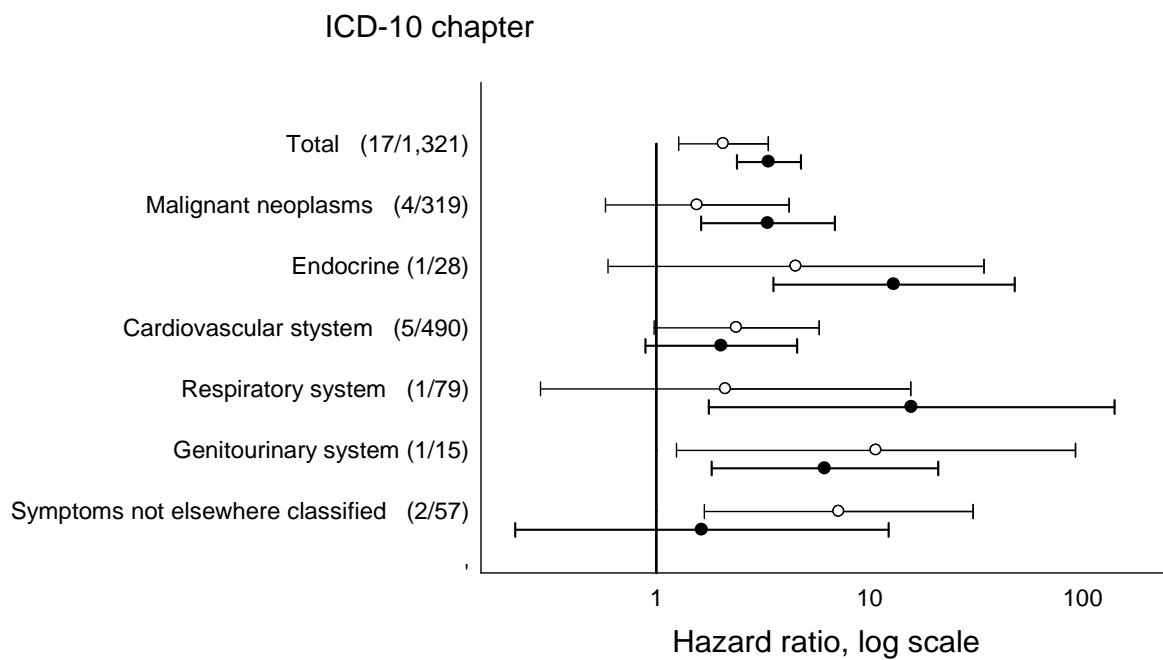


Figure 5

	Controls	47,XXX, mosaics included	p-value controls compared to 47,XXX	45,X	47,XXX mosaics excluded	46,XX/47,XXX	p-value comparing the karyotypes#
Total number of persons	10,297	108	-	831	62	46	-
Median age at diagnosis (range)	-	26.7 (0.0-73.2)	-	17.5 (0.0-85.5)	13.6 (0.0-65.0)	35.9 (0.0-73.2)	p<0.0001
Median year at birth (range)	-	1963 (1895-1992)	-	1966 (1886-1992)	1976 (1913-1992)	1951 (1895-1984)	p<0.0001
Median year at diagnosis (range)	-	1985 (1963-2008)	-	1986 (1962-2009)	1984 (1966-2008)	1986 (1963-2006)	p=0.47
Number with partnership (%)	7,685 (74.6)	67 (62.0)	p<0.005	313 (52.1)	31 (50.0)	36 (78.3)	p<0.005
Median age at first partnership (CI)*	25.0 (24.7-25.1)	25.1 (23.9-27.5)	p=0.67	24.5 (21.4-28.8)	24.5 (22.3-25.6)	28.3 (24.2-32.2)	p=0.10
Number of mothers (%)	5,657 (54.9)	49 (45.4)	p<0.05	181 (21.8)	21 (33.9)	28 (60.9)	p<0.005
Median age of mothers at birth of first child (CI)	24.0 (24.0-24.0)	26.0 (23.1- 27.0)	p=0.15	28 (27-29)	25.0 (21.4-27.0)	26.0 (22.6-27.7)	p=0.32
Number with at least one education* (%)	1,715 (29.6)	8 (12.9)	p<0.005	193 (34.5)	4 (9.5)	4 (25.0)	p=0.25
Retired persons* (%)	1,605 (18.4)	22 (26.8)	p=0.07	134 (19.9)	12 (24.5)	10 (28.6)	p=0.68
Median age at retirement* (CI)	59.9 (59.7-60.0)	39.8 (29.2-49.5)	p<0.0005	45.3 (32.9-56.0)	30.8 (21.7-48.1)	49.0 (30.3-62.8)	p=0.06
Number of persons with at least one conviction (%)	1,329 (12.9)	14 (13.0)	p=0.85	91 (11.0)	9 (14.5)	5 (10.9)	p=0.62

Table 1: Details regarding controls and 47,XXX syndrome persons.

Details regarding controls and 47,XXX syndrome persons, divided into two subgroups according to karyotype. For comparison, data on 45,X (Turner syndrome) are included. *Some did not have any registration at all; these persons are excluded from the following calculations. # The subgroup of 47,XXX excluding mosaics are compared with 46,XX/47,XXX. CI: 95% confidence interval.