Associations of psychiatric disorders with sex chromosome aneuploidies in the Danish iPSYCH2015 dataset: a case-cohort study

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Summary

Background Increased prevalence of mental illness has been reported in clinical studies of sex chromosome aneuploidies, but accurate population-based estimates of the prevalence and clinical detection rate of sex chromosome aneuploidies and the associated risks of psychiatric disorders are needed. In this study, we provide such estimates, valid for children and young adults of the contemporary Danish population.

Methods We used the iPSYCH2015 case-cohort dataset, which is based on a source population of single-born individuals born in Denmark between May 1, 1981, and Dec 31, 2008. The case sample comprises all individuals from the source population with a diagnosis of any index psychiatric disorder (schizophrenia spectrum disorder, bipolar disorder, major depressive disorder, autism spectrum disorder, or ADHD) by the end of follow-up (Dec 31, 2015), registered in the hospital-based Danish Psychiatric Central Research Register. The cohort consists of individuals randomly selected from the source population, and overlaps with the case sample. Biobanked blood samples for individuals in the case and cohort samples underwent genotyping and quality-control filtering, after which we analysed microarray data to detect sex chromosome aneuploidy karyotypes (45,X, 47,XXX, 47,XXY, and 47,XYY). We estimated the population-valid prevalence of these karyotypes from the cohort sample. Weighted Cox proportional hazards models were used to estimate the risks of each index psychiatric disorder associated with each sex chromosome aneuploidy karyotype, by use of date of first hospitalisation with the index disorder in the respective case group and the cohort as outcome. The clinical detection rate was determined by comparing records of clinical diagnoses of genetic conditions from the Danish National Patient Register with sex chromosome aneuploidy karyotype determined by our study.

Findings The assessed sample comprised 119 481 individuals (78 726 in the case sample and 43 326 in the cohort) who had genotyped and quality-control-filtered blood samples, including 64 533 (54%) people of gonadal male sex and 54 948 (46%) of gonadal female sex. Age during follow-up ranged from 0 to 34·7 years (mean 10·9 years [SD 3·5 years]). Information on ethnicity was not available. We identified 387 (0·3%) individuals as carriers of sex chromosome aneuploidies. The overall prevalence of sex chromosome aneuploidies was 1·5 per 1000 individuals. Each sex chromosome aneuploidy karyotype was associated with an increased risk of at least one index psychiatric disorder, with hazard ratios (HRs) of 2·20 (95% CI 1·42–3·39) for 47,XXY; 2·73 (1·25–6·00) for 47,XXX; 3·56 (1·01–12·53) for 45,X; and 4·30 (2·48–7·55) for 47,XYY. All karyotypes were associated with an increased risk of ADHD (HRs ranging from 1·99 [1·24–3·19] to 6·15 [1·63–23·19]), autism spectrum disorder (2·72 [1·72–4·32] to 8·45 [2·49–28·61]), and schizophrenia spectrum disorder (1·80 [1·15–2·80] to 4·60 [1·57–13·51]). Increased risk of major depressive disorder was found for individuals with 47,XXY (1·88 [1·07–3·33]) and 47,XYY (2·65 [1·12–5·90]), and of bipolar disorder for those with 47,XXX (4·32 [1·12–16·62]). The proportion of sex chromosome aneuploidy carriers who had been clinically diagnosed was 93% for 45,X, but lower for 47,XXY (22%), 47,XXX (15%), and 47,XYY (15%). Among carriers, the risk of diagnosis of at least one index psychiatric disorder did not significantly differ between those who had and had not been clinically diagnosed with sex chromosome aneuploidies (p=0·65).

Interpretation Increased risks of psychiatric disorders associated with sex chromosome aneuploidies, combined with low rates of clinical diagnosis of sex chromosome aneuploidies, compromise the adequate provision of necessary health care and counselling to affected individuals and their families, which might be helped by increased application of genetic testing in clinical settings.

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Research in context

Evidence before this study

Increased prevalence of mental illness has been reported in clinical studies of sex chromosome aneuploidies, but few population-based studies of the risk of psychiatric disorders associated with sex chromosome aneuploidies have been published. We searched MEDLINE to Oct 30, 2022, for studies published in English, containing combinations of the following terms: "psychiatric", "schizophrenia", "bipolar disorder", "major depression", "autism", or "ADHD"; with "association" or "risk"; and "45,X", "Turner syndrome", "47,XXX", "Trisomy X", "47,XXY", "Klinefelter syndrome", "47,XYY", or "Jacob's syndrome"; and "register" or "population". We identified only four population-based studies addressing the risk of psychiatric disorders for one or more sex chromosome aneuploidy karyotypes. Three of those studies reported an increased risk of psychiatric disorders. All four studies relied on register-based clinical diagnoses of sex chromosome aneuploidies, and therefore did not include the majority of individuals with sex chromosome aneuploidies, who are assumed to be clinically undetected.

Added value of this study

To the best of our knowledge, this is the first study combining data from nationwide biobanks and health registers to estimate the association of sex chromosome aneuploidy carriage (based on genotyping) with the risk of psychiatric outcomes in a population-representative manner. This design differs from that of previous population-based studies in including the large proportion of sex chromosome aneuploidy carriers in whom the condition has not been clinically detected (and who are, therefore, usually not included in studies based on clinical diagnosis of sex chromosome aneuploidies). All four sex chromosome aneuploidy karyotypes assessed in this study were found to be associated with an increased risk of psychiatric disorders, and these risks were similarly increased in sex chromosome aneuploidy carriers with and without clinical diagnosis of sex chromosome aneuploidies.

Implications of all the available evidence

Our results corroborate the increased prevalence and risks of psychiatric disorders reported for people with sex chromosome aneuploidies in most previous studies of selected clinical samples and register-based population studies of individuals with clinically detected sex chromosome aneuploidies. Our findings also show that sex chromosome aneuploidy carriers who remain without clinical detection of the condition are at a similarly increased risk of developing psychiatric disorders. Increased use of genetic testing in clinical settings could provide earlier diagnosis of emerging psychiatric complications in these individuals, and thereby increase the chances of a favourable treatment outcome.

Introduction

Sex chromosome aneuploidies are genetic conditions involving an atypical number of sex chromosomes relative to the typical 46,XY and 46,XX karyotypes. These conditions are usually caused by chromosomal non-disjunction occurring at meiosis or early postzygotic developmental stages.[1] The most common sex chromosome aneuploidies are 45,X and the three trisomies—47,XXX, 47,XXY, and 47,XYY—which have estimated frequencies of between 0·5 and 1·3 per 1000 livebirths,[2] although a high proportion of carriers of sex chromosome aneuploidies go undiagnosed.[1,3] Sex chromosome aneuploidies have no pathognomonic features and have great variability in penetrance and expressivity, but some of the most studied manifestations of sex chromosome aneuploidies include alterations of growth (short stature in 45,X and tall stature in sex chromosome trisomies),[4] gonadal function (ovarian dysgenesis in 45,X,[5] premature ovarian failure in 47,XXX,[6] and hypogonadism in 47,XXY),[7] and neurodevelopment.[1]

Over the past two decades, awareness of the associations between sex chromosome aneuploidies and neurodevelopmental and psychiatric impairments has grown.[8] However, neuropsychiatric characterisation of sex chromosome aneuploidies has lagged behind that of recurrent autosomal copy-number variants, despite sex chromosome aneuploidies involving dosage changes of more genes and being more prevalent[2] than most recurrent copy-number variants.[9,10] The best available research to date has reported high rates of several psychiatric disorders in studies of people with clinically diagnosed sex chromosome aneuploidies, including psychotic disorders (6–12%), autism (15–30%), and ADHD (30–70%) in people with sex chromosome trisomies,[11] and intellectual disability (5–10%), ADHD (25%), and anxiety or depression (50%) in people with 45,X.[12] Additionally, a study published in 2021 found clinically significant ADHD symptoms in 25 (24%) of 104 children aged 1–6 years with sex chromosome trisomy.[13]

The findings of the few published population-based studies in this field have mostly been consistent with those of clinical studies. Three population-based studies reported 2–6-times increased risks of psychiatric disorders associated with 45,X[14] and 47,XXY.[15,16] A fourth such study, of all four sex chromosome aneuploidy karyotypes, found evidence of increased risks of schizophrenia and bipolar disorder associated with 47,XYY when individuals with the two disorders were regarded as one case group.[17]

Despite the high collective prevalence of sex chromosome aneuploidies and evidence for their association with psychiatric impairments, two obstacles have hindered definitive understanding of the population-based associations between mental health outcomes and sex chromosome aneuploidies, posing a major challenge

to adequate health-care planning and provision for these conditions. First, the most recent prevalence estimates for sex chromosome aneuploidies from attempted full detection (in a sequential birth series)[2] are now more than 30 years old. Several factors that could potentially influence the prevalence of sex chromosome aneuploidies have changed during this period, including average maternal age and elective abortion in conjunction with prenatal screening.[18] As such, updated population-based prevalence estimates for sex chromosome aneuploidies are necessary to properly assess the scale of clinical need presented by these conditions. Second, to date, there have been no population-based estimates of the penetrance of sex chromosome aneuploidies for psychiatric outcomes from genetic studies. Securing such estimates is an especially high priority in sex chromosome aneuploidies because the rate of psychiatric disorders might differ between the minority of carriers of sex chromosome aneuploidies in whom the genetic condition is clinically detected, and the majority in whom it remains undetected.[1,3] Our previous work on recurrent copy-number variants using the Danish iPSYCH2012 case-cohort study design[19] showed that unbiased population-based samples obtained through nationwide health registers and biobanks are crucial for accurate estimation of psychiatric penetrance in under-diagnosed genetic conditions, and can substantially revise the penetrance estimates from studies involving traditional case-control samples[9] or registry-based studies of clinically diagnosed carriers.[10]

In the current study, we aimed to address these obstacles by leveraging the Danish iPSYCH2015 case-cohort[20] sample to study the four most prevalent sex chromosome aneuploidies (45,X, 47,XXX, 47,XXY, or 47,XYY), to estimate the prevalence and risk of psychiatric disorders among individuals affected by these genetic conditions, and directly contrast them with the corresponding age-matched and gonadal-sex-matched part of the Danish population. We also harnessed this study design to provide population-based estimates of the relative reproductive rate in people with sex chromosome aneuploidies, and screen for associations between sex chromosome aneuploidies and several other diagnoses not directly targeted by the iPSYCH2015 case-cohort design.

Methods

Study design

This study was done with use of the iPSYCH2015 case-cohort study sample,[20] which is an update and expansion of the iPSYCH2012 case-cohort study sample.[19] An overview of the iPSYCH2015 study design and its application in this study is given in the appendix (p 2). The study includes 141 265 individuals selected from all 1 657 449 singleton births that occurred in Denmark between May 1, 1981, and Dec 31, 2008, who were alive and residing in Denmark on their first birthday and had a mother registered in the Danish Civil Registration System.[21] The study has a dual design, involving a sample of cases and a cohort. The sample of cases comprised all individuals (n=93 608) with one or more of the following psychiatric disorders diagnosed and registered in the Danish Psychiatric Central Research Register (established in 1970)[22] no later than Dec 31, 2015: schizophrenia spectrum disorder (ICD-10 F20–F29; n=16 008), bipolar disorder (ICD-10 F30–F31; n=3819), major depressive disorder (ICD-10 F32–F33 and ICD-8 296.09, 296.29, 298.09, and 300.49; n=37 555), autism spectrum disorder (ICD-10 F84; n=24 975), or ADHD (ICD-10 F90; n=29 668). The cohort comprised 50 615 individuals drawn from the source population at random. The index psychiatric disorders were initially selected to represent common complex mental illnesses with childhood or early adult onset and illnesses that often have a common genetic component.

Because many individuals are diagnosed with more than one of the index disorders, the sum of the number of individuals across diagnostic groups is more than the case total of 93 608. Additionally, because the randomly drawn population sample naturally includes individuals with a diagnosis of mental illness, the numbers of individuals in the case sample and cohort sum to more than the overall study sample of 141 265, with 2958 individuals included in both the case sample and the cohort (appendix p 2).

For individuals in the case-cohort sample, all available biobanked blood samples underwent DNA extraction, genotyping, and quality-control filtering as part of the iPSYCH2012 and iPSYCH2015 studies, as described below. Individuals without available samples for genotyping or with samples that did not pass quality control were excluded from further study. Among the quality-control filtered samples (around 85% of those from the initial study sample), we identified sex chromosome aneuploidy karyotypes through analysis of microarray data.

This study follows the STROBE[23] guidelines on case-cohort studies.[24] Access to the data and its use for research purposes was granted by the Danish Scientific Ethics Committee, the Danish Health Data Authority, the Danish Data Protection Agency, and the Danish Neonatal Screening Biobank Steering Committee.

Genotyping and detection of sex chromosome aneuploidies

Genotyping was done with Illumina genotyping arrays (Illumina, San Diego, CA, USA) using whole-genome amplified DNA from dried neonatal blood spots extracted from the Danish Neonatal Screening Biobank.[25] The genotyping of iPSYCH2012 samples is described in detail elsewhere.[19] Sampling and genotyping of additional samples (iPSYCH2015i, which when combined with iPSYCH2012 constitutes the complete iPSYCH2015 case-cohort) differed in several ways;[20] most importantly, iPSYCH2015i samples were genotyped using the Global Screening Array version 2, whereas iPSYCH2012

See Online for appendix

samples had been genotyped using the PsychArray version 1.0.[19] Single-nucleotide polymorphism genotype calling and quality control were done with Illumina's GenTrain software tool for all samples that could be successfully identified and extracted from the Danish Neonatal Screening Biobank. The extraction of B-allele frequency as well as probe intensities (in the form of log-R-ratio) was done with Illumina GenomeStudio. Samples with a genotyping call rate below 95% were excluded from further study.[19]

We identified carriers of 45,X, 47,XXX, 47,XXY, and 47,XYY by analysing log-R-ratio and B-allele frequency using a two-stepped approach. First, we identified putative carriers by clustering samples based on mean log-R-ratio values for X and Y chromosomes (for samples registered as male), and for X and all autosomal chromosomes combined (for samples registered as female). Next, we visually inspected log-R-ratio and B-allele frequency profiles for X and Y chromosomes for all the putative carriers of sex chromosome aneuploidies to assess their sex chromosome carriage status (see appendix pp 3, 5, and 7 for more details).

Other available diagnoses and outcomes

Using diagnostic information obtained through the Danish Psychiatric Central Research Register[22] and the Danish National Patient Register[26] for other iPSYCH2015 studies, we assessed the risk associated with sex chromosome aneuploidies for a number of other disorders: intellectual disability, epilepsy, migraine, asthma, hernia, congenital malformation of the circulatory system, syncope, and febrile seizures. Further details on those analyses are provided in the appendix (p 8).

Diagnoses of sex chromosome aneuploidies from the Danish National Patient Register[26] were available for a subset of the iPSYCH2015 sample, and all comparisons between individuals with sex chromosome aneuploidies identified by genotyping in our study and individuals with clinically detected sex chromosome aneuploidies were done in this subset. We considered as clinically detected all individuals with an ICD-10 diagnosis of 45,X (Q96.0), 47,XXX (Q97.0), 47,XXY (Q98.0), 47,XYY (Q98.5), an unspecified Turner syndrome (Q96.9) or Klinefelter syndrome (Q98.4) diagnosis, and individuals with 47,XXX or 47,XYY with a diagnosis of sex chromosome anomaly not further specified (ICD-10: Q98.7 or Q98.8; ICD-8 759.5). We did not have access to records pertaining to prenatal detection among individuals with clinically detected sex chromosome aneuploidies.

Information on the number of offspring of individuals in the study sample by the end of 2015 (including any adopted children) were obtained from the Danish Civil Registration System.[21]

Statistical analysis

The risk of each of the five iPSYCH2015 index psychiatric disorders (schizophrenia spectrum disorder, bipolar disorder, major depressive disorder, autism spectrum disorder, and ADHD) associated with sex chromosome aneuploidies was assessed by weighted Cox proportional hazards models, with age at first hospitalisation for the index disorder as the outcome and sex chromosome aneuploidy status included as an independent variable. For each model, all individuals with the index disorder (cases) and all individuals from the cohort were included, without considering the case status of other index disorders (appendix p 2). Individuals were censored on whichever date occurred first: date of death; date of loss to follow-up or emigration; or Dec 31, 2015, if they had no relevant hospitalisation before that date. The models were fitted separately for each sex chromosome aneuploidy karyotype and in a gonadal sex-specific way for the karyotype in question (ie, 45,X and 47,XXX were tested against 46,XX; and 47,XXY and 47,XYY were tested against 46,XY). Population-unbiased risk estimates were obtained by computing inverse probability of sampling weights following Barlow's procedure.[27] The standard error and 95% CIs of the regression coefficient were computed using a robust estimator.[10]

To study the relative reproductive rate, we fitted a Poisson regression-type generalised additive model for each sex chromosome aneuploidy karyotype compared with the matching gonadal sex, with number of offspring at the end of follow-up as the outcome, excluding individuals who were younger than 16 years at the end of follow-up. Sex chromosome aneuploidy status was coded as the independent variable, and we adjusted for age by including a smoothed function of age at the end of follow-up as a covariate, allowing for a non-linear fit. All the five iPSYCH2015-targeted psychiatric disorders were also included in the model as separate covariates. All statistical analyses were done in R (version 3.3.1). The survival models were fitted with the survival R package.

To compare the population prevalence of sex chromosome aneuploidies in our study with that of the largest previous study,[2] we considered liveborn individuals with the corresponding karyotype (including mosaicism) in the previous study[2] and identified carriers of sex chromosome aneuploidies in our study. We tested the difference in each sex chromosome aneuploidy karyotype with a two-sided Fisher's exact test, and the trend across all sex chromosome aneuploidies with a Mantel-Haenzel test.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

After genotyping and quality-control filtering, 119 481 individuals with genotyped blood samples from the iPSYCH2015 case-cohort remained (appendix p 2), including 78 726 individuals in the case sample who were

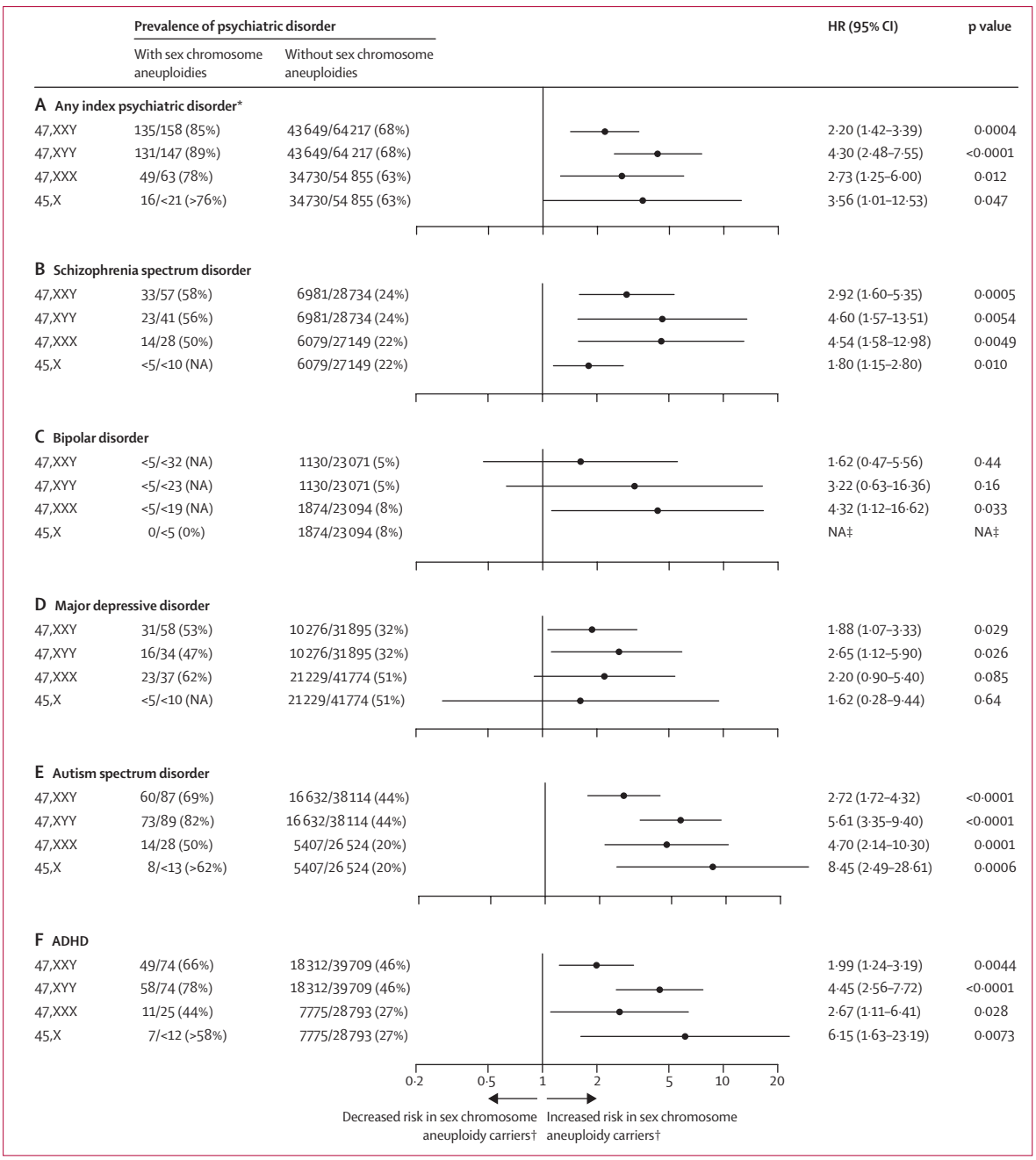

Figure 1: **Risks of psychiatric disorders by sex chromosome aneuploidy karyotype**
HRs and 95% CIs were estimated with population-weighted Cox proportional hazards models. Error bars are 95% CIs. Some data are provided in the form <X to prevent deduction of counts below five, which cannot be shown for legal reasons. HR=hazard ratio. NA=not applicable. *One or more of schizophrenia spectrum disorder, bipolar disorder, major depressive disorder, autism spectrum disorder, and ADHD. †Compared with individuals of the same sex without sex chromosome aneuploidies. ‡None of the 45,X carriers identified in the study had been diagnosed with bipolar disorder.

diagnosed with one or more of the index psychiatric disorders and 43 326 cohort individuals (3%) randomly drawn from the source population. The assessed sample included 64 533 (54%) people of male gonadal sex and 54 948 (46%) of female gonadal sex, and their age during follow-up (ie, from birth until 31 Dec, 2015) ranged from 0 to 34·7 years (mean of each individual during follow-up was 10·9 years [SD 3·5]). Among the 119 481 individuals with genotyped samples, we identified 387 (0·3%) as carriers of one of the four sex chromosome aneuploidy karyotypes under study (19 45,X, 63 47,XXX, 158 47,XXY, and 147 47,XYY).

Hospital records regarding chromosomal conditions, including any clinical diagnoses of sex chromosome

aneuploidies, were available for 73 646 individuals. Within this subset, we identified 240 individuals carrying sex chromosome aneuploidies, of whom 55 (23%) also had clinical diagnoses of sex chromosome aneuploidies. The clinical diagnosis rate was high for 45,X (93%), but low for 47,XXX (15%), 47,XXY (22%), and 47,XYY (15%). Mean age at clinical diagnosis was 10·6 years (SD 9·8) for 45,X; 10·1 years (6·7) for 47,XXX; 14·9 years (9·1) for 47,XXY; and 12·1 years (5·9 for 47,XYY). 24% of individuals with clinically diagnosed sex chromosome aneuploidies, mostly with Turner syndrome or Klinefelter syndrome, were not indicated as carriers on the basis of our single-nucleotide polymorphism array-based approach, with evidence that these individuals were likely to be enriched for non-canonical gene dosage alterations (appendix p 7).

The risk of diagnosis of any one of the five psychiatric disorders was significantly increased for individuals with one of the four sex chromosome aneuploidy karyotypes compared with individuals without these genetic conditions, with hazard ratios (HRs) ranging from 2·20 (95% CI 1·42–3·39; for 47,XXY) to 4·30 (2·48–7·55; for 47,XYY; figure 1).

All sex chromosome aneuploidies were associated with an increased risk of the two disorders with primarily childhood onset, autism spectrum disorder and ADHD, with risks being lowest in individuals with 47,XXY and highest in those with 45,X for both of these psychiatric disorders (figure 1). All four sex chromosome aneuploidies were also associated with an increased risk of schizophrenia spectrum disorder. Additionally, 47,XXY and 47,XYY were associated with an increased risk of major depressive disorder, and 47,XXX was associated with an increased risk of bipolar disorder (figure 1).

The combined fraction of the five psychiatric disorders did not differ significantly between carriers of sex chromosome aneuploidies with and without a clinical diagnosis of sex chromosome aneuploidy (p=0·65).

The combined population prevalence of the four sex chromosome aneuploidies was 1·45 (95% CI 1·13–1·85) per 1000 individuals of the respective gonadal sex (estimated in the full cohort). Population prevalence (per 1000 individuals of the respective gonadal sex) was <0·23 for 45,X, 0·65 for 47,XXX, 0·81 for 47,XYY, and 1·23 for 47,XXY (figure 2; table). Although none of the prevalence estimates for individual sex chromosome aneuploidies differed from those previously reported[2] (p>0·05 for each sex chromosome aneuploidy), when combined they had a lower prevalence than that reported in the previous study (2·06, 95% CI 1·63–2·58; p=0·046).

47,XXX, 47,XXY, and 47,XYY were associated with reduced relative reproductive rates (estimated as number of offspring in a Poisson regression model; figure 3). No offspring were recorded among the 19 identified individuals carrying 45,X, which is consistent with the well characterised ovarian dysgenesis in 45,X.[5]

From available hospital records relating to the eight other disorders present in two or more carriers of a given sex chromosome aneuploidy karyotype (other than the five iPSYCH2015 index psychiatric disorders; appendix p 8), we observed a highly increased risk of congenital

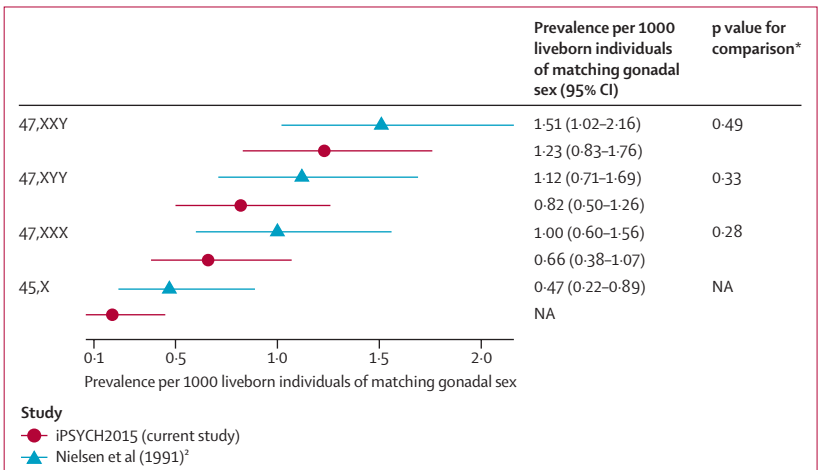

Figure 2: **Prevalence of sex chromosome aneuploidies in Denmark**
Prevalence estimates per 1000 individuals of matching gonadal sex of the four sex chromosome aneuploidy karyotypes in the iPSYCH2015 random population cohort, compared with those of a previous population-based study.[2] Error bars are 95% CIs. NA=not applicable. *Comparison between studies.

	Assessed samples, female: male	45,X (prevalence per 1000)	47,XXX (prevalence per 1000)	47,XXY (prevalence per 1000)	47,XYY (prevalence per 1000)
Any index psychiatric disorder*	34 803: 43 923	16 (0·46)	49 (1·41)	135 (3·07)	131 (2·98)
Schizophrenia spectrum disorder	6095: 7040	<5	14 (2·30)	33 (4·66)	23 (3·27)
Bipolar disorder	1878: 1135	<5	<5	<5	<5
Major depressive disorder	21 259: 10 325	<5	25 (1·17)	34 (3·29)	16 (1·55)
Autism spectrum disorder	5432: 16 768	8 (1·47)	14 (2·58)	60 (3·58)	73 (4·35)
ADHD	7795: 18 420	7 (0·90)	11 (1·41)	49 (2·66)	58 (3·15)
Cohort	21 297: 22 029	<5	14 (0·66)	27 (1·23)	18 (0·82)

The sex chromosome aneuploidy karyotype count is shown for each disorder with prevalence per 1000 of the corresponding gonadal sex in parentheses. Due to legal restrictions, we cannot show the exact number or prevalence of sex chromosome aneuploidies in diagnosis groups including fewer than five carriers. *Individuals diagnosed with one or more of the specified disorders.

Table: **Total sample and carrier counts by sex chromosome aneuploidy karyotype and iPSYCH2015 case-cohort subgroup**

malformations of the circulatory system associated with 45,X (HR 30·61 [95% CI 9·71–96·13]), and moderate increases (HRs ranging from 1·77 [1·21–2·60] to 3·74 [2·26–6·18]) in the risk of intellectual disability, syncope, febrile seizures, asthma, hernia, and migraine associated with one or more sex chromosome aneuploidy karyotypes (appendix pp 4, 6).

Discussion

This study extends understanding of sex chromosome aneuploidy karyotypes in several important ways. To our knowledge, it is the first study to provide population-based estimates of the risk of psychiatric disorders associated with sex chromosome aneuploidies and simultaneously consider the four most common sex chromosome aneuploidy karyotypes detected through genotyping. Previous estimates of enrichment of psychiatric diagnoses in sex chromosome aneuploidies have mainly been derived from diagnostic surveys in groups of individuals with clinical diagnoses of sex chromosome aneuploidies[11–13] or from registry-based research[14–17] (also relying solely on carriers of clinically detected sex chromosome aneuploidies). Our prevalence estimates of each sex chromosome aneuploidy karyotype are consistent with those reported earlier for the Danish population,[2] although a statistically significantly lower prevalence was observed for the four sex chromosome aneuploidies combined.

The most important finding of this study is that of an overall increased risk of the index psychiatric disorders associated with all four sex chromosome aneuploidy karyotypes. These findings are largely consistent with those of previous studies of sex chromosome aneuploidies,[11–17] but add important context in several ways. For example, the associated HRs are of similar or even higher magnitude than those observed in many rarer gene-dosage disorders that have a longer-standing history as models of genetic risk in psychiatric research (eg, 22q11.2 deletion and copy-number variants at 16p11.2).[9,10] This observation highlights the relative impact of sex chromosome aneuploidies as genomic disorders that contribute significantly to the risk of psychiatric disorders at a population level.

In concordance with previous reports,[1,3] we found that 47,XXY, 47,XYY, and 47,XXX had been clinically detected in only a small proportion of carriers. Importantly, a test across all four karyotypes showed no indication that the subset of carriers with clinically detected sex chromosome aneuploidies had higher rates of psychiatric disorders.

An important strength of the iPSYCH2015 study is its case-cohort design with a unique ability to genetically assess sex chromosome aneuploidy karyotypes in a well powered, population-representative sample of individuals with and without psychiatric disorders. Previously, because of the low clinical detection rate of sex chromosome aneuploidies (particularly the trisomies 47,XXX, 47,XXY, and 47,XYY), it has not been clear whether the increased rates of psychiatric disorders observed in individuals with clinically detected sex chromosome aneuploidies would also apply to undetected carriers.

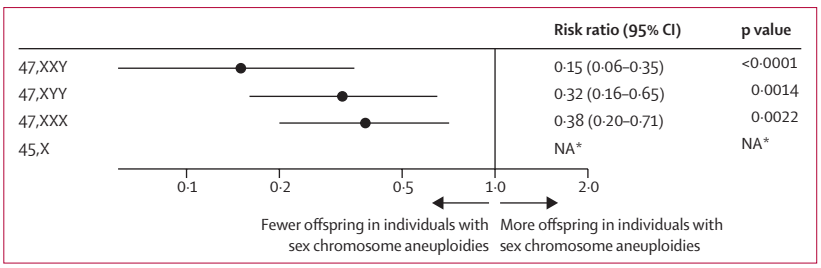

Figure 3: **Association of sex chromosome aneuploidies with relative reproductive rate**
Risk ratios and corresponding 95% CIs were estimated as the relative change in number of offspring compared with individuals of the same gonadal sex without sex chromosome aneuploidies, obtained by fitting a Poisson regression model, accounting for age at end of follow-up and psychiatric case status. NA=not applicable. *A model could not be fitted for 45,X because no offspring were observed among carriers.

We observed an increased risk of bipolar disorder associated with 47,XXX. To the best of our knowledge, this is the first reported association of this kind, although a recent study of 74 individuals with 47,XXX reported increased rates of affective and psychotic disorders, including bipolar disorder.[28] Notably, most studies of sex chromosome aneuploidies have focused on children and adolescents, and risk estimates for most disorders with typically adult onset have therefore been scarce.

Taken together, our findings highlight a uniform increased risk of major psychiatric disorders associated with sex chromosome aneuploidies, and a missed opportunity for early diagnosis and treatment intervention, particularly in individuals with 47,XXX or 47,XYY karyotypes, which have low clinical detection rates and are associated with substantially increased risks of major psychiatric disorders, including ADHD, autism spectrum disorder, and schizophrenia spectrum disorder.

Despite low power to assess the changes in relative reproductive rate associated with sex chromosome aneuploidies because of the young age of the case-cohort sample during follow-up, we observed substantial reductions in the number of offspring associated with all three sex chromosome trisomies (no offspring were recorded for 45,X carriers). Although factors other than fertility influence the reproductive rate, this large relative reduction in number of offspring is consistent with the late or compromised gonadal development and inadequate hormonal levels commonly noted in carriers of sex chromosome aneuploidies.[1,5–7]

In our analysis of other outcomes available for the iPSYCH2015 sample, we replicated several previously reported associations, including with congenital heart defects in 45,X,[5] intellectual disability in 47,XXX,[6] and seizure-related disorders and asthma in 47,XYY.[29] We also observed indications of increased risk for a few other disorders, not previously reported. However, these disorders were not part of the iPSYCH2015 case-cohort design, and, because we only assessed risk for disorders

presenting in at least two carriers of a given sex chromosome aneuploidy, the associated risk estimates might be inflated and should only be considered as suggestive.

In the Cox proportional hazards analysis, each hazard function was estimated separately and only in the subset of samples with the gonadal sex corresponding to the sex chromosome aneuploidy karyotype. Although this means that we cannot directly test differences in psychiatric risk patterns across sex chromosome aneuploidy karyotypes in our sample, a few karyotype-based features are noteworthy, and could have implications for clinical and basic science if confirmed in a formal comparative analysis.

One notable karyotype-based feature we observed was a nominally greater increase in the risk of psychiatric disorders in 47,XXX than in 47,XXY. The biological basis for this differential effect of X-chromosome gain in people of female sex versus those of male sex is unclear and warrants further research. Paradoxically, studies of gene expression in the peripheral tissues of people with sex chromosome aneuploidies suggest that X-chromosome gain induces a substantially greater transcriptomic disruption in male versus female cells,[30] which is counter to the observed risk levels for psychiatric outcomes. However, we lack functional genomic studies of the effects of sex chromosome aneuploidies on human brain tissue, which would arguably be more relevant for understanding potential differences in psychiatric penetrance between sex chromosome aneuploidy subtypes. In future studies, it would be important to examine mechanisms beyond cis-regulatory effects by which sex chromosome aneuploidies could affect cellular functions, such as altered dosages of non-genic regulatory elements,[31] broader disruptions of nuclear architecture,[32] and changes in cell division rates.[33]

Another karyotype-based feature we observed was the nominally greater risk of psychiatric outcomes associated with 47,XYY than with 47,XXY, which accords with earlier studies of clinical samples.[34,35] This risk pattern might seem unlikely given that X-chromosome gain leads to substantially greater changes in gene dosage and brain anatomy[36] than Y-chromosome gain does. However, other potential sources of divergence in psychiatric risk profiles across the sex chromosome trisomies might explain this difference. These sources include impaired gonadal function (seen in 47,XXY, and less so in 47,XXX, but not in 47,XYY), and interactions between X-chromosome dosage and different biological contexts in people of male sex (XY background and testes) versus those of female sex (XX background and ovaries).

Notwithstanding the disparate directions and magnitudes of effect of X-chromosome and Y-chromosome dosages on total brain size,[37] neuroanatomical studies have revealed that supernumerary X and Y chromosomes exert spatially overlapping effects on regional brain anatomy, which might theoretically underpin the shared increases in psychiatric risk reported in this study. Specifically, increases in both X-chromosome and Y-chromosome dosages are associated with the contraction of frontotemporal cortices and expansion of parieto-occipital cortices,[37–39] in addition to reductions in the relative sizes of several cerebellar[36] and subcortical[40] regions.

Although the population-representative design of the iPSYCH2015 case-cohort study and the leverage of nationwide health registers have many advantages, our study has some limitations. For example, although bloodspot-based genotyping enables powerful population-based detection of genetic conditions such as carriage of sex chromosome aneuploidies, it has limited ability to detect mosaic aneuploidies and partial sex chromosome alterations. Around a third of individuals with clinically diagnosed Turner syndrome and a quarter of those with clinically diagnosed Klinefelter syndrome were not indicated as carriers of sex chromosome aneuploidies in our analysis. Among those with Turner syndrome, mean age at diagnosis was higher in individuals who were not identified compared with those who were identified by our analysis as carrying a 45,X karyotype, and most of those not identified had an unspecified Turner syndrome diagnosis (ICD-10 Q96.9), suggesting that they might not be 45,X carriers. By contrast, diagnosis subtype and age at diagnosis of Klinefelter syndrome did not differ between individuals identified and not identified as carrying 47,XXY in our analyses, suggesting that at least some could be true 47,XXY carriers not detected by our analysis.

Although the design of the iPSYCH2015 study optimises its power to assess the risk of the index psychiatric disorders associated with sex chromosome aneuploidies in a population-representative manner, the study's power to estimate associated risks of other outcomes, including those of mental disorders that are not specifically targeted in the design, is low. Additionally, the relatively young age of participants during follow-up limits the study's power to analyse disorders (including index disorders such as bipolar disorder) that have a late typical age at onset.

Finally, the study relies on diagnoses from a nationwide hospital-based register of inpatients and outpatients,[25] which does not include information on individuals who are diagnosed and treated for psychiatric illness solely by general practitioners or privately practising psychiatrists. Therefore, a subset of milder instances of psychiatric illness (given that severe forms of illness most often will be diagnosed and treated in a hospital) are likely to have been missed from the sample.

In conclusion, the combination of increased risks of psychiatric disorders and low clinical detection rates for three of the four sex chromosome aneuploidy karyotypes (with a mean age at clinical diagnosis ranging from 9 to 14 years for the few individuals with clinically detected sex chromosome aneuploidies) suggests that most carriers of these genetic conditions might not

receive appropriate clinical care. Increased use of genetic testing in clinical settings could promote early diagnosis, inform on the risk of illness and complications associated with sex chromosome aneuploidies, and increase the likelihood of positive treatment outcomes for people with psychiatric disorders.

Contributors

XCS, TW, and AI designed the study. TW and AI led the study. XCS, SM, MV, and AI performed the genomic analyses of sex chromosome aneuploidies. WKT and DH designed and conducted the epidemiological analyses. XCS, SM, MV, MDK, WKT, AR, DH, TW, and AI contributed to interpretation of results. XCS wrote the initial draft, and XCS, AB, AJS, WKT, AR, DH, TW, and AI completed the manuscript. All authors contributed to, read, and approved the final manuscript. TW and AI had full access to the data and take responsibility for the integrity of the data and the accuracy of the analysis.

Declaration of interests

We declare no competing interests.

Data sharing

Regarding access to study data (other than sensitive person-level data, which by requirement of the data custodian and Danish legislation cannot be shared) please contact the corresponding author.

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