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Neurodevelopmental and Mental Health Outcomes in a National Clinical Sample of Youth With Sex Chromosome Trisomies Compared With Matched Controls

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ABSTRACT

Objective: To compare the prevalence of neurodevelopmental and mental health diagnoses in a national sample of youth with sex chromosome trisomies (SCTs) with matched controls.

Methods: Patients in PEDSnet and a diagnosis code mapping to 47,XXY/Klinefelter syndrome (n = 1171), 47,XYY/Double Y syndrome (n = 243), or 47,XXX/Trisomy X syndrome (n = 262) were matched with controls using propensity scores. Generalized estimating equations computed odds ratios (OR) with 95% confidence intervals (CI) for the prevalence of diagnoses within the neurodevelopmental and mental health composites, psychotropic medication prescriptions, and encounters with behavioral health and therapy providers. Alpha was set at 0.0025 to account for multiple comparisons.

Results: Patients with SCTs had higher odds of diagnoses within the neurodevelopmental (OR 6.3, 95% CI, 5.7–7.2) and mental health composites (OR 2.7, 95% CI, 2.3–3.2) compared with matched controls. All neurodevelopmental diagnoses were more prevalent among all SCT groups compared with controls. Within the mental health composite, only the prevalence of anxiety and mood disorder was higher in all SCT groups. A higher proportion of patients with SCTs had psychotropic prescriptions compared with controls (stimulants 13.1% vs 5.2%, selective serotonin reuptake inhibitors 8.7% vs 2.8%, antipsychotics 6.5% vs 2.4%, $p < 0.0001$ for all). Overall, 48% of patients with SCTs had a clinical encounter with a behavioral health provider vs 16.6% of controls (OR 5.6, 95% CI, 4.1–5.1).

Conclusion: Compared with matched controls, youth with SCTs receiving care at US tertiary care pediatric centers have disproportionately high rates of neurodevelopmental and mental health conditions, emphasizing the need for appropriate screening and intervention in these populations.

Index terms: sex chromosome aneuploidies, Klinefelter syndrome, Trisomy X, 47,XXY, 47,XYY, 47,XXX, PEDSnet, Jacobs syndrome

Sex chromosome trisomies (SCTs), an additional X or Y chromosome, occur in ~1 in 500 live births but historically are profoundly underdiagnosed. The most common of these is 47,XXY, also known as Klinefelter syndrome (XXY), with an incidence of 1 in 600 men and an estimated lifetime clinical ascertainment of ~35%, with less than half of these before

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adulthood.[1,2] The other 2 SCTs, 47,XYY (XYY) and 47,XXX (XXX), occur in ~1 in 1000 individuals, but fewer than 10% receive a clinical diagnosis. Consequentially, our knowledge of the SCT clinical phenotype is largely based on a narrow minority who have received genetic testing and elect to participate in clinical research that occurs at only a few centers across the world.[3] The widespread adoption of prenatal cell-free DNA screening is estimated to greatly increase the number of infants recognized to have SCTs,[4] emphasizing the urgency for additional research on these conditions in childhood to guide counseling and care practices.

An extra X or Y is associated with several neurodevelopmental and mental health comorbidities. While cognitive abilities typically fall within the average range, developmental delays, learning disabilities, and mood disorders are frequently appreciated. Birth cohort studies originating in the 1960s reported that ~70% of children with SCTs had developmental delays and required early intervention services.[5,6] More recently, SCTs have been associated with an increased risk for autism spectrum disorder (ASD), with research cohorts showing that up to 15% of youth with XXX, 18% with XXY, and 30% with XYY meeting full criteria for ASD and as many as 50% having social communication deficits that range from mild to severe.[7–11] The prevalence of attention deficit hyperactivity disorder (ADHD) ranges from 11% to 52% of individuals with SCTs.[8,12,13] Mental health diagnoses have also been reported to be more prevalent within this population, with ~27% of men with XXY experiencing clinical anxiety and depressive disorders and up to 12% meeting Diagnostic and Statistical Manual (DSM) criteria for a psychotic disorder.[9,13–17]

Though these studies consistently illustrate the presence of neurodevelopmental and mental health comorbidities in SCTs, it is important to note that most have been conducted in single centers with convenience samples, likely leading to selection bias toward participants who are experiencing concerns. Furthermore, there is often not a control population, so the actual risk of these conditions for youth with their SCTs compared with their peers remains unknown. We aimed to fill this gap by using a large pediatric clinical health system in the United States to compare the prevalence of neurodevelopmental and mental health diagnoses, psychotropic medication prescriptions, and encounters with behavioral health and therapy providers among youth with XXY, XYY, and XXX with matched controls to guide clinicians caring for youth with SCTs in counselling, diagnosis, and management of neurodevelopmental and mental health conditions.

METHODS

Data Source

Deidentified electronic health record (EHR) data elements were acquired from PEDSnet (https://PEDSnet.org/), a pediatric Learning Health System infrastructure with a Common Data Model based on standard terminologies.[18] At the time of data acquisition, PEDSnet consisted of ~6 million patients seen at 1 of 6 geographically diverse pediatric health care organizations including our institution, Children's Hospital Colorado, Nationwide Children's Hospital, Children's Hospital of Philadelphia, St. Louis Children's Hospital, Nemours Children's Health System, and Seattle Children's Hospital. This project was approved by the PEDSnet Data Coordinating Center and was determined to be Non-Human Subjects Research by our ethics committee (protocol #18-0887).

Sample Inclusion Criteria

All patients within PEDSnet with a billing or problem list diagnosis mapping to 47,XXY/Klinefelter syndrome, 47,XYY/Double Y syndrome, or 47,XXX/Trisomy X syndrome (Supplemental Digital Content 1, Table S1, http://links.lww.com/JDBP/A483) without other chromosome disorders (SNOMED code 409709004) and at least 1 outpatient encounter from 2009 to 2019 were identified as SCT cases. Individuals with male sex and diagnoses for both 47,XXY and 47,XYY (n = 38) were individually reviewed and assigned to either XXY or XYY based on the number of XXY and XYY codes, the type of encounter for each, and presence of hypogonadism. Approximately 200,000 randomly selected patients within PEDSnet with at least 1 outpatient encounter and no diagnoses mapping to any genetic conditions were obtained for the control pool.

Matching Procedure

Comparison of demographic variables that could influence the outcomes of interest revealed significant differences between cases and the control pool; therefore, we proceeded with propensity score matching. Each SCT case was matched to 4 controls using a greedy match algorithm with a 0.10 wide caliper based on propensity score for sex, birth year, age at last encounter, duration in PEDSnet, site, race, ethnicity, and insurance type. Missingness for categorical variables was handled by including missing as a category. The standardized difference after matching yielded an excellent balance for all variables (Supplemental Digital Content 2, Figure S1, http://links.lww.com/JDBP/A480, Supplemental Digital Content 3, Figure S2, http://links.lww.com/JDBP/A481, Supplemental Digital Content 4, Figure S3, http://links.lww.com/JDBP/A482).

Outcome Definitions

The primary outcomes were the prevalence of any neurodevelopmental diagnosis (neurodevelopmental diagnosis composite) and any mental health diagnosis (mental health diagnosis composite). These composite outcomes based on SNOMED terminology hierarchy (www.snomed.org) were refined by experienced clinicians to combine related concepts and eliminate overlap (Supplemental Digital Content 1, Table S1, http://links.lww.com/JDBP/A483). Secondary outcomes included related diagnoses of interest that did not fall under the neurodevelopmental or mental health composites (self-harm composite, sleep disorders, and substance abuse disorders). One or more diagnoses of interest documented on the patient's problem list or a coded billing diagnosis within the EHR was considered affirmative of having that condition. For all diagnoses, PEDSnet concept IDs were mapped to SNOMED using Athena Ancestor Tables (developed by Observational Health Data Sciences and Informatics, Columbia University).

To corroborate the diagnostic outcomes data, we also evaluated relevant prescriptions and encounters. Any prescription for stimulant, selective serotonin reuptake inhibitor (SSRI), or antipsychotic medication was evaluated as these are the recommended first-line treatment for ADHD, anxiety and depression, and mood and behavioral stabilization, respectively. Encounters for behavioral health specialists and therapists were also analyzed. Specific criteria and codes for all binary outcomes are defined in Supplemental Digital Content 1, Table S1, http://links.lww.com/JDBP/A483.

Statistical Analyses

Continuous variables are reported as mean and SD if data were normally distributed and median with interquartile range (IQR) if not normally distributed. We calculated the number and percentage of individuals positive for each binary outcome; a minimum of 11 individuals were needed to report specific values per PEDSnet policy. We used generalized estimating equation (GEE) models to compare the differences in prevalence for the outcomes of interest between cases and matched controls while accounting for possible correlation between cases and controls introduced with the matching procedure and age at last visit as a covariate. Odds ratios (OR) with 95% confidence intervals (CI) were computed. Owing to suspected phenotypic differences between SCT groups and disproportionate sample sizes, the 3 SCT groups were stratified and analyzed independently. Post-hoc sensitivity analyses included stratifying by patient age (<6 vs ≥ 6 years [school-age] at last visit), encounter with a behavioral health provider, and presence of a diagnosis relevant to specific medications (i.e., ADHD diagnosis for stimulant medications, any mental health condition for SSRI or antipsychotic medication). To account for multiple comparisons, the conservative Bonferroni correction was applied for 20 unique outcomes resulting in an alpha of 0.0025 for statistical significance. SAS version 9.4 (SAS Institute Inc, Cary, NC, USA) was used to perform statistical analysis, and Prism Graphpad version 10.2.1 was used to construct figures.

RESULTS

A total of 1676 individuals with SCTs were identified and included in this analysis, with approximately 5 times as many patients with 47,XXY/Klinefelter syndrome than with 47,XYY or 47,XXX. The age at first visit with an SCT diagnosis was older in XXY (median 8, IQR 1–13 years) than XYY (5, 1–10) and XXX (4, 0–10) groups. SCT cases were well-matched to the control group on demographic and clinical variables aside for the number of outpatient encounters within the PEDSnet system, which was higher in SCT cases (Table 1). Individuals had an average of 4 years of clinical data and represented a range of PEDSnet sites, race, ethnicity, and payor categories.

Overall, 52.2% of individuals with SCT had 1 or more diagnoses within the neurodevelopmental composite, representing 6.3 times greater odds compared with controls (95% CI, 5.7–7.2). The OR for the neurodevelopmental composite in XXY was lower and CIs did not overlap with the other trisomy conditions; therefore, stratified results are presented in Table 2 and Figure 1A. All neurodevelopmental conditions were more prevalent in individuals with SCTs compared with matched controls, although feeding delays did not reach our a priori threshold for significance within the XYY and XXX groups (Fig. 2B). The most common neurodevelopmental diagnoses were motor delay and the speech and language disorder composites, with each being recorded in 25% of boys with XXY, ~40% of boys with XYY, and ~30% of girls with XXX. This equated to an OR for motor delays of 3.1 (95% CI, 2.6–3.6) in XXY, 6.1 (4.3–8.6) in XYY, and 9.1 (6.0–13.7) in XXX and an OR for speech and language disorder 4.2 (3.6–5.0), 7.7 (5.5–10.7), and 9.0 (6.2–13.2), respectively. The next most frequent was a diagnosis of ADHD, identified in 21.3% of boys with XXY, 32.5% of boys with XYY, and 17.6% of girls with XXX versus the prevalence among male and female controls of ~9% and 3% respectively, yielding OR of 2.8 in XXY (95% CI, 2.38–3.33), 5.2 (3.6–7.40) in XYY, and 7.0 in XXX (4.3–11.3). Less common but still more prevalent among SCT cases were ASD (XXY 10.8%, OR 2.9 [2.3–3.7]; XYY 25%, OR 8.0 [5.3–12.1]; XXX 8.8% OR 7.7 [3.9–15.3]) and intellectual developmental disorder (XXY 6.5%, OR 5.3 [3.7–7.4]; XYY 10.3%, OR 10.0 [4.3–8.6]; XXX 5%, OR 5.2 [2.3–12.7]). With age group stratification, ADHD and intellectual developmental disorder were only significant in the ≥ 6 years group, as expected based on diagnostic best practices.

Fewer individuals in this SCT cohort had mental health diagnoses (13.7%); however, these odds were still 2.7 times higher than sex and age-matched controls (95% CI, 2.3–3.2). Similar results were found for all 3 SCT groups (Table 2, Fig. 1B). Anxiety disorder was the most prevalent mental health condition for all 3 SCT, affecting 11.3% of boys with XXY, 13.2% of boys with XYY, and 19.8% of girls with XXX compared with 4% of male controls and 7% of female controls (XXY OR 2.3 [95% CI, 1.9–2.7], XYY 3.7 [2.3–6.1], XXX 4.2 [2.8–6.2]). Mood disorder diagnoses were documented for 8% to 10% of individuals with SCTs, significantly more than found for controls (4%–5%). Of the specific mood disorders examined, only depression in XXY reached staticial significance (OR 1.6 [95% CI, 1.2–2.1]). Although not included under the mental health composite, sleep disorder diagnoses were documented in 11% of all individuals with SCTs, yielding OR of 1.4 (1.2–1.8) in XXY and 1.9 in both XYY and XXX (95% CI, 1.3–2.8 and 1.3–3.0 respectively). With age group stratification, differences in anxiety, mood, and sleep disorders only remained significant within the older group. Diagnoses of disorders of impulse control, adjustment, psychosis, tics, eating, and personality were uncommon overall and too small to be reported for XYY and XXX groups. In XXY, adjustment disorder and personality disorder were significantly higher in the older cohort, affected 1% to 3% of individuals (Table 2). Self-harm behaviors and substance abuse diagnoses were uncommon in all groups.

The proportion of patients with prescriptions for stimulant (13.1% vs 5.2%), SSRI (8.7% vs 2.8%) and antipsychotic medications (6.5% vs 2.4%) were higher for all SCT groups compared with controls ($p < 0.0001$ for all, Fig. 2A and Supplemental Digital Content 1, Table S2, http://links.lww.com/JDBP/A483). When limiting the sample just to those with relevant diagnoses, there were no differences in the proportion with ADHD who had been prescribed stimulants. However, more individuals with XXY and a mental health diagnosis had been prescribed an SSRI and/or antipsychotic compared with controls with mental health diagnoses (Fig. 2B).

Approximately half of individuals with SCT had 1 or more behavioral health encounters within the PEDSnet system compared with 17% of controls (Fig. 2C, Supplemental Digital Content 1, Table S3, http://links.lww.com/JDBP/A483). Odds of an encounter was nearly 4-fold greater in youth with XXY (OR 3.9, 95% CI, 3.4–4.4) and 7-fold in XYY and XXX (95% CI, 5.3–9.6 and 5.0–9.3, respectively). However, once care with a behavioral health specialist was established, the number of visits per individual was similar (Fig. 2C, Supplemental Digital Content 1, Table S3, http://links.lww.com/JDBP/A483). There was a strong association between having an encounter with a behavioral health provider and a diagnosis falling within the neurodevelopmental or mental health composite ($p < 0.0001$ for all SCT groups). However, even patients who did not have a behavioral health encounter still had greater odds of neurodevelopmental diagnoses compared with controls, but odds of mental health disorders were no longer different (data not

Table 1.

Demographic Characteristics of Youth With SCT and Matched Controls

	XXY/Klinefelter		XYY/Double Y		XXX/Trisomy X	
	Cases (n = 1171)	Controls (n = 4684)	Cases (n = 243)	Controls (n = 972)	Cases (n = 262)	Controls (n = 1048)
PEDSnet site, n (%)						
Site 1	101 (8.6)	415 (8.9)	22 (9.1)	114 (11.7)	15 (5.7)	52 (5.0)
Site 2	239 (20.4)	903 (19.3)	42 (17.3)	173 (17.8)	58 (22.1)	237 (22.6)
Site 3	120 (10.2)	485 (10.4)	16 (6.6)	63 (6.5)	23 (8.8)	93 (8.9)
Site 4	348 (29.7)	1381 (29.5)	73 (30.0)	278 (28.6)	66 (25.2)	256 (24.4)
Site 5	283 (24.2)	1154 (24.6)	77 (31.7)	290 (29.8)	88 (33.6)	360 (34.4)
Site 6	80 (6.8)	346 (7.4)	13 (5.3)	54 (5.6)	12 (4.6)	50 (4.8)
Race, n (%)						
White	801 (68.4)	3218 (68.7)	173 (71.2)	714 (73.5)	181 (69.1)	710 (67.7)
Black	110 (9.4)	456 (9.7)	17 (7.0)	69 (7.1)	17 (6.5)	71 (6.8)
Asian	43 (3.7)	145 (3.1)	QI	19 (2.0)	QI	28 (2.7)
Other[a]	121 (10.3)	489 (10.4)	30 (12.3)	106 (10.9)	32 (12.2)	123 (11.7)
Unknown	96 (8.2)	376 (8.0)	18 (7.4)	64 (6.6)	24 (9.2)	116 (11.1)
Ethnicity, n (%)						
Hispanic	127 (10.8)	516 (11.0)	36 (14.8)	142 (14.6)	33 (12.6)	110 (10.5)
Non-Hispanic	948 (81.0)	3794 (81.0)	193 (79.4)	785 (80.8)	209 (79.8)	838 (80.0)
Unknown	96 (8.2)	374 (8.0)	14 (5.8)	45 (4.6)	20 (7.6)	100 (9.5)
Insurance, n (%)						
Public	367 (31.3)	1474 (31.5)	85 (35.0)	341 (35.1)	84 (32.1)	331 (31.6)
Private	720 (61.5)	2860 (61.1)	141 (58.0)	554 (57.0)	167 (63.7)	671 (64.0)
Other	66 (5.6)	225 (4.8)	15 (6.2)	62 (6.4)	QI	31 (3.0)
Unknown	18 (1.5)	125 (2.7)	QI	15 (1.5)	QI	15 (1.4)
Age at first outpatient encounter in years, median (IQR)	4.1 (0.4–11.0)	4.5 (0.8–10.4)	2.0 (0.1–6.9)	2.0 (0.3–6.6)	1.2 (0.1–7.3)	2.0 (0.2–7.6)
Age at last outpatient encounter in years, median (IQR)	13.4 (6.1–17.8)	13.4 (8.0–16.7)	10.2 (4.0–15.8)	10.4 (5.0–14.8)	8.5 (3.3–14.8)	9.1 (3.7–14.8)
<6 yrs, n (%)	295 (25.2)	850 (18.1)	86 (35.3)	293 (30.1)	101 (38.5)	372 (35.5)
≥6 yrs, n (%)	903 (77.1)	3942 (84.2)	167 (68.7)	719 (74.0)	161 (61.4)	676 (64.5)
Duration in PEDSnet in years, median (IQR)	4.9 (1.5–10.3)	5.3 (1.2–10.6)	4.7 (1.4–9.7)	4.9 (1.2–10.1)	4.0 (1.1–7.6)	3.2 (0.5–8.4)
Number of outpatient encounters, median (IQR)	10.0[b] (4.0–23.0)	6.0 (2.0–16.0)	11.0[b] (4.0–30.0)	6.0 (2.0–16.0)	8.5[b] (4.0–25.0)	5.0 (2.0–13.0)
No. of encounters with SCT diagnosis, median (IQR)	5.0 (2.0–11.0)	—	3.0 (2.0–7.0)	—	4.0 (2.0–8.0)	—
Age at first encounter with SCT diagnosis in years, median (IQR)	8.0 (1.0–13.0)	—	5.0 (1.0–10.0)	—	4.0 (0.0–10.0)	—
Age at last encounter with SCT diagnosis in years, median (IQR)	12.0 (5.0–17.0)	—	8.0 (3.0–14.0)	—	7.0 (2.0–13.0)	—

[a] Includes more than 1 race.
[b] Significantly different between SCT cases and their respective controls.
IQR, interquartile range (25th–75th percentile); QI, quantity insufficient; numbers <11 cannot be reported per PEDSnet policy; SCT, sex chromosome trisomy.

shown). Individuals in all SCT cohorts were more likely to engage in any ancillary therapy (17% XXY, 25% XYY, 26% XXX vs 5%–7% controls), including occupational, physical, and speech therapies (Fig. 2C, Supplemental Digital Content 1, Table S4, http://links.lww.com/JDBP/A483).

DISCUSSION

In this cross-sectional analysis of a large, nationally representative clinical sample, youth with SCTs were more likely to be diagnosed with neurodevelopmental and mental health diagnoses compared with matched controls. These diagnostic results are corroborated with higher odds of behavioral health encounters and psychotropic prescriptions. Overall, our findings enhance existing literature from smaller studies suggesting vulnerabilities in these areas by adding OR compared with peers without SCTs. Furthermore, the study cohort is more diverse in race (>30% non-White) and socioeconomic status (>30% public insurance) compared with previous SCT studies. The high prevalence of neurodevelopmental and mental health conditions observed in this broad clinical sample reinforces the need for routine behavioral health evaluations through adolescence for youth with SCTs.

Each of the individual neurodevelopmental diagnoses were observed more frequently among individuals with SCTs compared with controls, with the highest estimates in XYY and XXX groups. We suspect the disparities we observed between SCT groups most likely reflect differing clinical ascertainment of SCT in our cohort. Although the overall prevalence of XXY is only slightly more than XYY and XXX, XXY is much more frequently clinically ascertained due to hypogonadism,[2] which was certainly true in our sample as the number of individuals with a diagnosis of XXY was 5 times the other SCT groups. Similarly, the median age at first encounter with a SCT diagnosis was older in XXY, reflecting the additional individuals diagnosed in puberty. As XYY and XXX do not have associated hypogonadal sequelae, clinical ascertainment is weighted toward neurodevelopmental concerns in early childhood. In addition, the XYY and XXX groups were younger than the XXY cohort when first receiving medical care within the PEDSnet system. Many early developmental concerns are less likely to be used as a billing diagnosis in older children and adolescents, even if an early history of delays was present. Additional research is needed to determine if the

Table 2.

Prevalence of Neurodevelopmental and Mental Health Diagnoses in Youth With SCT

	XXY/Klinefelter			XYY/Double Y			XXX/Trisomy X		
	Cases (n = 1171)	Controls (n = 4684)	GEE *p*	Cases (n = 243)	Controls (n = 972)	GEE *p*	Cases (n = 262)	Controls (n = 1048)	GEE *p*
Neurodevelopmental diagnoses									
Neurodevelopmental composite	543 (46.4)	850 (18.1)	<0.0001[a]	174 (71.6)	181 (18.6)	<0.0001	158 (60.3)	106 (10.1)	<0.0001[a]
Developmental delay composite	144 (12.3)	144 (3.1)	<0.0001[a]	49 (20.2)	34 (3.5)	<0.0001[a]	46 (17.6)	23 (2.2)	<0.0001[a]
Motor delay composite	298 (25.4)	471 (10.1)	<0.0001[a]	104 (42.8)	107 (11.0)	<0.0001[a]	72 (27.5)	42 (4.0)	<0.0001[a]
Feeding delay composite	53 (4.5)	100 (2.1)	<0.0001[a]	18 (7.4)	36 (3.7)	0.0162	18 (6.9)	33 (3.1)	0.0078
Speech and language composite	296 (25.3)	346 (7.4)	<0.0001[a]	96 (39.5)	76 (7.8)	<0.0001[a]	85 (32.4)	53 (5.1)	<0.0001[a]
Autism spectrum disorder	89 (7.6)	132 (2.8)	<0.0001[a]	44 (18.1)	29 (3.0)	<0.0001[a]	23 (8.8)	13 (1.2)	<0.0001[a]
ADHD	250 (21.3)	412 (8.8)	<0.0001[a]	79 (32.5)	83 (8.5)	<0.0001[a]	46 (17.6)	31 (3.0)	<0.0001[a]
Disruptive behavior disorder	170 (14.5)	253 (5.4)	<0.0001[a]	50 (20.6)	51 (5.2)	<0.0001[a]	35 (13.4)	26 (2.5)	<0.0001[a]
Learning disorder composite	115 (9.8)	86 (1.8)	<0.0001[a]	30 (12.3)	14 (1.4)	<0.0001[a]	33 (12.6)	QI	<0.0001[a]
Intellectual developmental disorder	76 (6.5)	61 (1.3)	<0.0001[a]	25 (10.3)	11 (1.1)	<0.0001[a]	13 (5.0)	QI	<0.0001[a]
Mental health diagnoses									
Mental health composite	146 (12.5)	288 (6.1)	<0.0001[a]	39 (16.0)	52 (5.3)	<0.0001	44 (16.8)	53 (5.1)	<0.0001[a]
Adjustment disorder	34 (2.9)	51 (1.1)	<0.0001[a]	QI	14 (1.4)	0.27	QI	11 (1.0)	0.68
Anxiety disorder	132 (11.3)	254 (5.4)	<0.0001[a]	32 (13.2)	38 (3.9)	<0.0001[a]	52 (19.8)	52 (5.0)	<0.0001[a]
Eating disorder	13 (1.1)	39 (0.8)	0.35	QI	QI	0.1	QI	QI	0.0014[a]
Impulse control disorder	19 (1.6)	QI	<0.0001[a]	QI	QI	0.0066	QI	QI	0.06
Mood disorder	92 (7.9)	227 (4.8)	<0.0001[a]	25 (10.3)	37 (3.8)	0.0002[a]	22 (8.4)	40 (3.8)	0.0024[a]
Depressive disorder	64 (5.5)	166 (3.5)	0.002[a]	11 (4.5)	22 (2.3)	0.07	15 (5.7)	36 (3.4)	0.08
Bipolar disorder	11 (0.9)	34 (0.7)	0.46	QI	QI	0.0003[a]	QI	QI	0.0003[a]
Personality disorder	13 (1.1)	16 (0.3)	0.0016[a]	QI	QI	0.0016[a]	QI	QI	>0.99
Psychotic disorder	12 (1.0)	16 (0.3)	0.0041	QI	QI	0.0167	QI	QI	0.2
Tic disorder	15 (1.3)	67 (1.4)	0.7	QI	15 (1.5)	0.17	QI	QI	0.49
Other related diagnoses									
Sleep disorders	111 (9.5)	318 (6.8)	0.0015[a]	39 (16.0)	89 (9.2)	0.0011[a]	35 (13.4)	77 (7.3)	0.0018[a]
Self-harm composite	23 (2.0)	47 (1.0)	0.0071	QI	QI	0.0007[a]	QI	12 (1.1)	0.0131
Substance abuse	11 (0.9)	33 (0.7)	0.41	QI	QI	>0.99	QI	QI	>0.99

All data are shown as number (%).
[a] Significant at an alpha of 0.0025 for comparison between SCT cases and their respective controls using GEE models accounting for matching and age at last visit.
ADHD, attention deficit hyperactivity disorder; GEE, generalized estimating equation; QI, quantity insufficient; numbers <11 cannot be reported per PEDSnet policy; SCT, sex chromosome trisomy.

neurodevelopmental phenotype truly differs between SCTs or if our observation is due to these ascertainment biases.

Developmental delays, language-based learning disabilities, and social communication deficits are well-documented in individuals with SCTs.[6–11] Birth cohort studies reported that language and/or motor delays affected >70% of children with SCTs.[5,19] Our results yield more modest estimates of delays, with a similar proportion of motor and language-related delays. Even

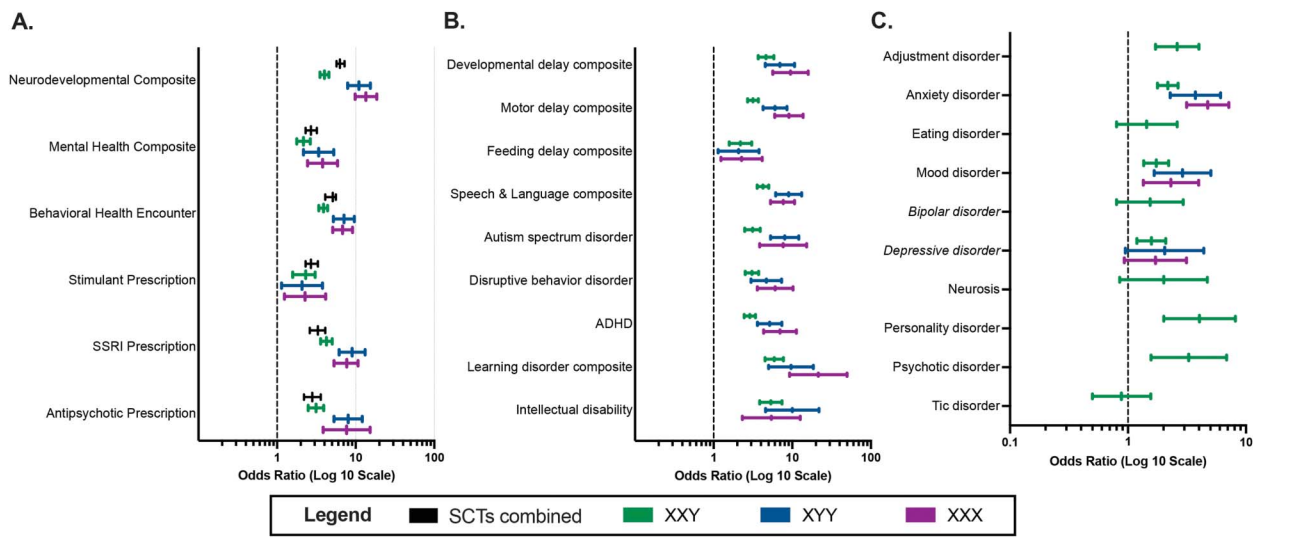

Figure 1. Forest plot with OR and 95% CI of A, primary outcomes, B, neurodevelopmental outcomes, and C, mental health outcomes for individuals with SCT when compared with matched controls on a log 10 scale. The italicized diagnoses are subgroups of the diagnoses directly above. Per PEDSnet policy, diagnoses with <11 individuals in case or control groups are not shown. ADHD, attention deficit hyperactivity disorder; CI, confidence intervals; OR, odds ratios; SCT, sex chromosome trisomy; SSRI, selective serotonin reuptake inhibitor.

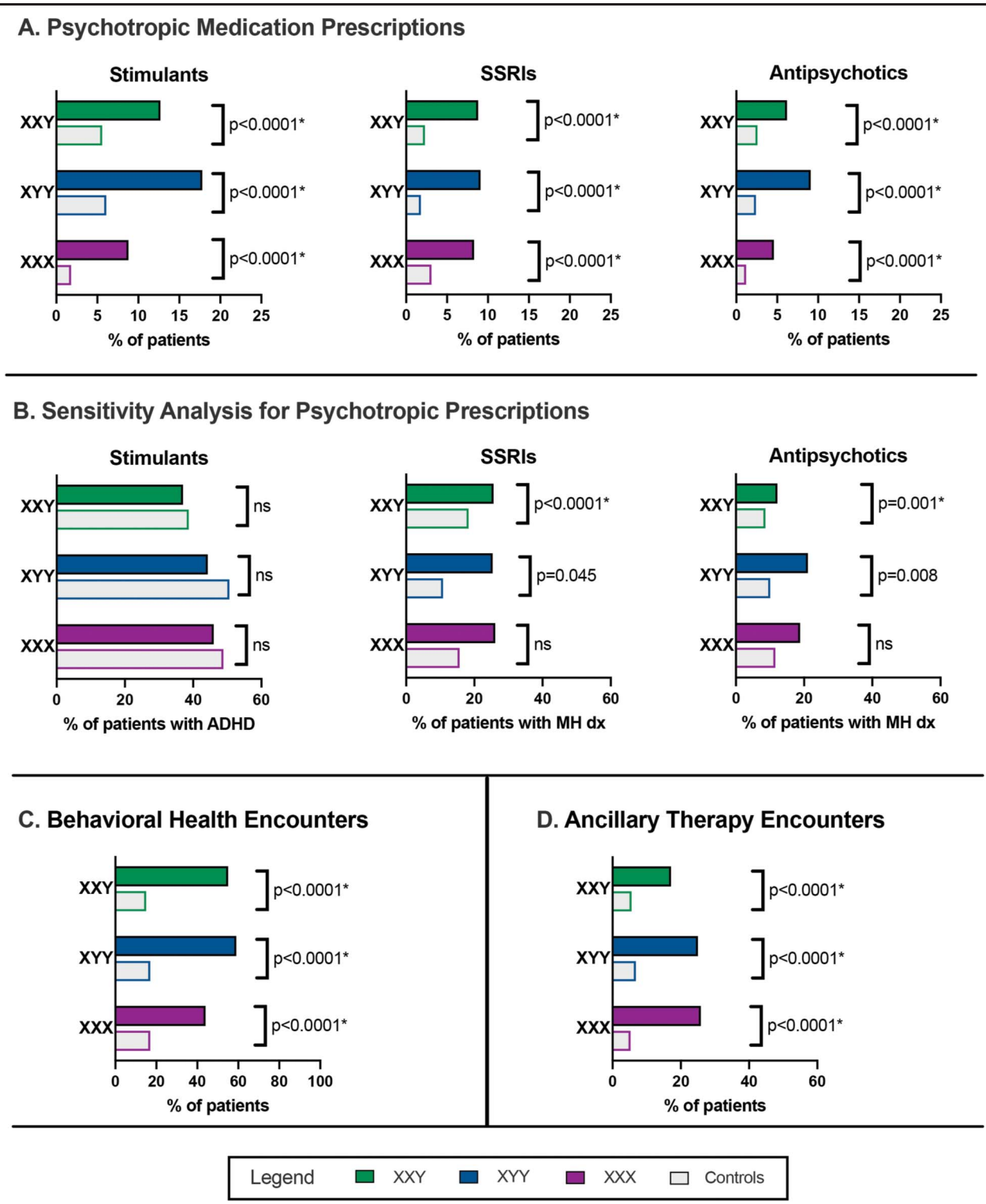

Figure 2. A, Proportion of individuals with SCT (colored bars) and their matched controls (white bars) with 1 or more prescriptions for medications falling under the stimulant (left), SSRI (middle), and antipsychotic (right) drug classes. B, Proportion of individuals with ADHD with and without SCT prescribed stimulants (left). Proportion of individuals with mental health diagnoses with and without SCT prescribed SSRIs (middle) or antipsychotics (right). C, Proportion of individuals with 1 or more behavioral health encounter within the PEDSnet system (left). D, Proportion of individuals with a physical, occupational, and/or speech therapy encounter. *Indicates statistical significance at an a priori alpha of 0.0025, although all *p*-values <0.05 are presented. ADHD, attention deficit hyperactivity disorder; MH dx, mental health diagnosis; ns, not significant; SCT, sex chromosome trisomy; SSRI, selective serotonin reuptake inhibitor.

so, our observation that 25% to 43% of children with SCTs in this unselected clinic sample have a billing diagnosis code of developmental delays (3–9 times higher than their peers) strongly supports that these are populations at high-risk for developmental delays. Many high-risk populations benefit from early intervention and automatically qualify for state services[20,21];

however, this is not universal for SCTs, and prospective studies are still needed to quantify the benefit for this population.

Other neurodevelopmental diagnoses also had lower prevalence estimates here compared with previous research. ASD was diagnosed in 5.7% to 18% of our cohort compared with 15% to 30% of other pediatric studies.[7–11,22] Learning disorder diagnoses were even more discrepant at 10% to 12% compared with >60% in previous estimates.[8,11,23,24] Our lower prevalence estimates for these outcomes may be explained by reliance on billing diagnoses within the PEDSnet EHR, thus not capturing outside clinic or community/school-based diagnoses or those lacking any diagnosis due to access issues. Therefore, these data may underestimate the true prevalence, though previous studies also probably overestimate it due to selection bias. Nevertheless, our observed higher odds of these conditions in SCT groups compared with the control cohort are likely to be reliable given that systematic limitations would affect cases and controls similarly.

Given that ADHD is often treated with medications, it is more likely to be accurately documented in the EHR than other neurodevelopmental diagnoses. Attention deficits with or without hyperactivity are suggested to be present in up to 11% to 50% of pediatric SCT samples.[8,12,13,25,26] Our data confirm that individuals with SCTs receive a clinical diagnosis of ADHD more frequently than their peers. When a diagnosis of ADHD was present, stimulants were prescribed to a similar proportion of SCT cases and controls. Further research is needed to determine if ADHD symptoms respond to stimulants in individuals with SCT as they do in the general population.

Mental health diagnoses were also more common in all 3 SCT genotypes, though there was variability between specific diagnoses. Most studies examining anxiety and depression in SCT cohorts report rates of both are higher than the general population.[8,13,25,27,28] Furthermore, adult studies suggest that individuals with SCTs are at risk for more complex psychiatric illnesses such as bipolar disorder and schizophrenia.[22,27] Our results confirm that youth with SCT had higher odds of anxiety and mood disorder diagnoses, along with higher odds of SSRI and antipsychotic prescriptions compared with their matched controls. However, we observed very few cases of bipolar or psychotic disorders, likely reflecting the young age of our cohort. Age of presentation for these and other mental health conditions in individuals with SCT should be further evaluated. Interestingly, among individuals with a mental health diagnosis, those with SCT were more often prescribed an SSRI or antipsychotic compared with controls. Future research could test whether mental health conditions in SCT are associated with more functional implications leading to higher medication use, and consider if medication use may be more likely accepted as a treatment option due to the presence of known genetic difference.

Finally, our data support that youth with SCTs are more likely to be connected to behavioral health and ancillary therapies within the PEDSnet system. Unsurprisingly, behavioral health encounters were positively associated with a diagnosis within the neurodevelopmental and/or mental health composites. Our data limit our ability to determine causality of this relationship, but we suspect that it is bidirectional. These data emphasize the importance of a multidisciplinary approach to care in this population.

While the use of EHR datasets such as PEDSnet allows for large sample sizes, rigorous matching procedures, and use of real-world, clinically meaningful outcomes, it also poses unique limitations for this study. First, youth being seen in tertiary care pediatric centers have more complex concerns, potentially oversampling for neurodevelopmental and mental health diagnoses among both cases and controls. However, our study is arguably more generalizable than other studies that specifically recruit youth with SCTs to study neurodevelopment and psychosocial outcomes. Next, our SCT sample is limited to patients with a clinical diagnosis prior to age 18, which is the minority of individuals with SCTs, largely reflecting those with an incidental prenatal diagnosis and those diagnosed secondary to early neurodevelopmental delays. We unfortunately cannot determine the reason for genetic testing, confirm the genotype, or evaluate for mosaicism. We did previously conduct a validation study for the accuracy of a diagnosis of Turner syndrome within PEDSnet, which was >90%,[29] and most of the reasons for false positives are not applicable to SCT; therefore, we anticipate a higher diagnostic accuracy for SCT.

As previously mentioned, we relied on billing diagnoses and other discrete data elements within the EHR, which is prone to errors of omission and commission. Diagnoses made and/or managed outside the PEDSnet system (including community or school-based services) will not be reflected. Furthermore, health and behavioral codes or free text within a note would not be captured, likely underestimating the prevalences reported within. We also are unable to confirm whether DSM-5[30] criteria were met in those with any given diagnosis within their EHR. Similarly, we acknowledge that reducing complex neurodevelopmental and mental health factors into binary outcomes fails to capture more granular details important in SCT conditions. Finally, conditions occurring in fewer than 1% of individuals with XXY or 5% of those with XYY and XXX could not be analyzed per PEDSnet data restrictions (minimum of 11 counts per cell) and larger datasets would be needed to inform risk for these rarer conditions in SCT. Despite these limitations, this study offers a valuable population-based perspective of neurodevelopmental and mental health diagnoses among youth with SCTs in the United States.

In conclusion, youth with SCTs in the PEDSnet database are more likely than their peers to be diagnosed with neurodevelopmental and mental health conditions. This is the first study to evaluate medical records in a large clinical sample of youth from multiple institutions across the United States. These results support universal evaluation of neurodevelopment and mental health in children with SCTs to facilitate early diagnosis and access to care. Future directions with PEDSnet or similar secondary datasets can explore mediators and moderators of neurodevelopmental and mental health outcomes, change over time, and intervention practices that may differ for youth with SCTs.

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