

Mental health and neurodevelopment in children and adolescents with Turner syndrome

Women's Health
Volume 18: 1–8
© The Author(s) 2022
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/17455057221133635
journals.sagepub.com/home/whe


Jeanne Wolstencroft¹ , William Mandy² and David Skuse¹

Abstract

Objectives: Turner syndrome (TS) is a rare sex chromosome aneuploidy, with an incidence of four in 10,000 new-born girls. TS is often associated with impaired social communication skills, but the extent to which these are attributable to Autism Spectrum Disorders (ASD) is uncertain. We made standardized assessments of the mental health and associated neurodevelopmental disorders in children and adolescents with TS and report on the prevalence of concurrent conditions.

Methods: Our sample comprised 127 girls with TS, 5–19 years of age. We obtained reports of their mental health from a combination of diagnostic interview (the Development and Wellbeing Assessment (DAWBA)), from the Strengths and Difficulties Questionnaire (SDQ) and from the Social Responsiveness Scale (SRS-2). Sources of information included parents, teachers and self-reports. The prevalence of mental health disorders in this sample was compared with age/sex matched national English data from typical controls.

Results: Most individuals with TS (83%) had experienced significant social communication difficulties and nearly one in four (23%) met diagnostic criteria for ASD on the DAWBA. One-third (34%) had at least one mental health or neurodevelopmental condition, and those girls with an ASD were at a greater risk of a co-occurring emotional disorder and/or attention deficit hyperactivity disorder (ADHD).

Conclusion: Children and adolescents with TS are substantially more likely to meet criteria for ASD than their typically developing peers. Our finding has clinical implications for appropriate behavioural management from preschool through to adolescence.

Keywords

autism, rare disorder, sex chromosome, turner syndrome, women's health

Date received: 12 April 2022; revised: 12 September 2022; accepted: 30 September 2022

Introduction

Turner syndrome (45, X; TS) is a common sex chromosome aneuploidy, with an incidence of 4 in 10,000 female births.¹ The physical phenotype is well-described; morbidities affect nearly every bodily system. These include dysmorphic features, skeletal abnormalities such as short stature, hearing difficulties, infertility, cardiac abnormalities, diabetes and thyroid problems.² However, relatively little research has been conducted on the psychological wellbeing of females with TS compared to studies of their physical health.³

Many women with TS experience lifelong difficulties in their social relationships,^{2,4,5} which are reminiscent of

those experienced by people with an autism spectrum disorder (ASD). Both Creswell and Skuse⁶ and a recent Swedish patient registry study found an increased risk of clinically significant ASD in girls and women with TS.⁷

¹The Great Ormond Street Institute of Child Health, University College London, London, UK

²Division of Psychology and Language Sciences, University College London, London, UK

Corresponding author:

Jeanne Wolstencroft, The Great Ormond Street Institute of Child Health, University College London, 30 Guilford Street, London WC1N 1EH, UK.

Email: j.wolstencroft@ucl.ac.uk



Traits of autism have also been documented by several investigations^{8–10} using tools such as the Autism Diagnostic Interview,⁶ the Childhood Autism Rating Scale¹¹ and the Social Responsiveness Scale.^{8–10} Nonetheless, there is controversy about the basis of social difficulties associated with the syndrome, which some have attributed to excessively short stature, unusual physical appearance or social anxiety rather than a fundamental impairment in the processing of social cues.^{2,12} Obtaining a better understanding of autistic traits in TS is of clinical importance: there is increasing recognition that such traits are also often overlooked in typically developing girls and young women.¹³ The benefit of early identification of impaired social communication skills and the provision of appropriate management for ASD traits is well established.¹⁴ Early intervention is associated with gains in cognition, language and adaptive behaviour, as well as improvements in daily living skills and social behaviour.¹⁵

Research into the most appropriate intervention to ameliorate social difficulties is viewed as a research priority by the TS community,³ yet no systematic assessment of psychosocial development in children has been made since 2001,¹⁶ and no survey of adult mental health since 2004.¹⁷ More recent studies have focused on specific problems such as attention deficit hyperactivity disorder (ADHD), depression or social anxiety but have lacked a comprehensive evaluation of risk in childhood or adulthood.^{6,18–24} A comprehensive and systematic evaluation of mental health and neurodevelopment in TS could lead to more effective and holistic care, enabling affected individuals to experience a better quality of life.

This study aimed to make a comprehensive evaluation of psychopathology, including neurodevelopmental conditions, associated with TS in girls and young women between 5 and 19 years. Our focus was primarily, but not exclusively, on the assessment of ASD traits. We employed a range of screening instruments, including a comprehensive diagnostic interview and a screening questionnaire for which we have comparison data on a representative sample of the general population. We used instruments that were employed in English national studies of young people's mental health in 1999, 2004 and 2017.^{25–28} These were supplemented by standardized measures of autistic traits and social interaction difficulties, rated by parents, teachers and by self-report.

Methods

Participants

Participants included both children and adolescents with Turner Syndrome (confirmed by genetic reports or clinic letters) aged 5–19 years. They were either members of the UK Turner Syndrome Support Society or attended specialist National Health Service (NHS) clinics at University College London Hospital and Great Ormond Street Hospital. There were no additional exclusion criteria. In a

subset of families, we obtained additional information from the child's classroom teacher. All participated in the SOAR Study (SOcial skills And Relationships in Turner Syndrome) from September 2016 to November 2019.

We used normative comparison data collected as part of the English national surveys of child and adolescent mental health in 2004 and 2017.^{26,29,30} These data were accessed from NHS Digital and the UK Data Archive Service.^{29,30}

Procedures

This study employed a cross-sectional observational study design. Parents and young people above the age of 12 were invited to self-complete psychometric questionnaires online or in pen and paper form. If consent was obtained, teachers were contacted to complete psychometric questionnaires too. Ethical approval for the SOAR study was obtained through the University College London Ethics Committee and the NHS West London Research Ethics Committee (UCL REC: 11837/001; IRAS: 219817). Participants under the age of 16 were asked to sign an assent form and their parent or legal guardian signed an additional parent consent form. Young people aged 16 and over consented to take part on their own behalf and signed an adult consent form.

Measures

Development and Wellbeing Assessment. The Development and Wellbeing Assessment (DAWBA) is an online comprehensive interview with parents. It was used to collect information on the child's behavioural adjustment and mental health, including friendships. The DAWBA has been used both in UK national and international surveys to assess child mental health in those aged between 5 and 19 years.^{25–28} Interpretation of DAWBA data was standardized, in accordance with *DSM-5* diagnostic criteria. The assignment of DAWBA diagnoses has high inter-rater reliability in studies of typical children^{25,27,31,32} and in children with neurodevelopmental disorders.³³ Clinical ratings in children attending a Social Communication Disorders Clinic have been validated against a comprehensive multidisciplinary assessment, using gold standard instruments, and it has been shown to have excellent sensitivity (93.3%) and specificity (78.6%).³⁴ The Mental Health of Children and Young People in England 2017 survey data for girls aged 5 to 19 was used as a comparison sample. Descriptions of the cohort and sampling procedures are available from NHS Digital.³⁰

Strengths and Difficulties Questionnaire. The Strengths and Difficulties Questionnaire (SDQ) is a well-validated behavioural screening questionnaire.³⁵ It includes subscales which measure emotional symptoms, conduct problems, hyperactivity, peer relationship problems and prosocial behaviour. Appropriate versions were completed online by

Table 1. Prevalence of DAWBA diagnoses: UK national study of typically developing (TD) girls and girls with TS.

Disorder prevalence (%)	TS girls n = 100	TD girls n = 3,803	RR	TS with DAWBA ASD n = 23	TS without DAWBA ASD n = 77	RR
Any disorder	34	12.9	2.64	–	–	–
Emotional disorders	13	10	1.3	26.1	9.1	2.9
<i>Anxiety disorders</i>	13	9.1	1.4	26.1	9.1	2.9
Separation anxiety disorder	2	0.6	3.33	0	2.6	0
Generalized anxiety disorder	7	1.8	3.88	21.8	2.6	8.4
Obsessive compulsive disorder	1	0.4	2.5	0	1.3	0
Specific phobia	3	0.9	3.33	4.3	2.6	1.7
Social phobia	2	1.1	1.82	0	2.6	0
<i>Depressive disorders</i>	1	2.8	0.36	4.3	0	–
Major depressive episode	1	2	0.5	4.3	0	–
Attention deficit hyperactivity disorder (ADHD)	13	0.6	21.6	39.1	5.2%	7.5
Autism spectrum disorder (ASD)	23	0.4	57.5	100	0	–
Eating disorders	1	0.7	1.43	0	1.3	0
Tics/other less common disorders	2	0.6	3.33	8.7	0	–

TS: Turner Syndrome; TD: Typically Developing; RR: Relative Risk; DAWBA: Development and Wellbeing Assessment.

the parents and teachers, and self-reports were obtained from adolescents (Table 1). Subscales measuring emotional and behavioural problems can be combined to create a Total Difficulties score. An additional impact scale measures adjustment in daily life. SDQ data collected in the Mental Health of Children and Young People in Great Britain 2004 national study data of girls aged 6 to 16 was obtained from the UK Data Service,^{26,29} and were used for comparison purposes.

Social Responsiveness Scale, Second Edition. The Social Responsiveness Scale, Second Edition (SRS-2) was completed online by parents and teachers to measure the severity of autistic symptomatology. The SRS-2 has convergent validity with ASD diagnostic instruments such as the Autism Diagnostic Observation Schedule™ (ADOS) and Autism Diagnostic Interview, Revised (ADI-R).^{36–38} The SRS-2 subscales measure Social Awareness, Social Cognition, Social Communication, Social Motivation, and Restricted Interests and Repetitive Behaviour. Raw scores are converted into T-scores which are normed for age and sex. T-scores in the ‘mild’ range are indicative of clinically significant deficits in reciprocal social behaviour that have a mild to moderate impact on everyday social interactions. T-scores in the ‘moderate’ range are indicative of substantial deficits in everyday social interaction and typically associated with ASD of moderate severity. T-scores in the ‘severe’ range are considered to be strongly associated with a clinical diagnosis of an ASD. Norms are available for the SRS-2 from age 2.5 to 79 years.

Indices of Multiple Deprivation. Socioeconomic status was measured using postcode data using the Indices of Multiple Deprivation (IMD).³⁹ IMD scores combine information from seven distinct domains to produce a relative deprivation rank. The domains include income, education, employment, crime, health, barriers to housing and services, and the living environment. IMD scores are ranked and organized into deciles; the first decile includes the most deprived areas and the 10th decile includes the least deprived areas.

Results

Participants

A total of 127 families consented to take part in the study; this included 127 parents (one per proband), 44 young people and 30 teachers. 37% of participants were recruited through specialist NHS Turner syndrome clinics (n=47) and 63% of families were recruited from the UK Turner Syndrome Support Society (n=80). The distribution of socioeconomic status of the participants, as measured by IMD scores, was skewed towards relatively less deprived centiles (deciles 1–5=34%; deciles 6–10=66%).

78.7% of parents completed the DAWBA (n=100), 75.6% completed the SDQ (n=96) and 81.9% completed the SRS-2 (n=104). 75% of eligible young people contributed by answering a self-report questionnaire (n=33) and 30 teachers returned at least one completed questionnaire. Participants themselves approached teachers about taking part; therefore, the number of teachers who declined is not known.

The sample comprised a wide range of TS karyotypes, which were representative of the TS population¹ (Supplemental Table S1). We were not able to verify the karyotype of 18 participants. Data from participants with unconfirmed karyotypes were included in the final analysis as they obtained a similar range of scores on the SDQ and SRS-2, and their DAWBA profiles were also comparable to those of the remaining sample.

Mean participant age was 12.1 years ($SD=4.4$). By late adolescence, all were taking oestrogen replacement therapy, which was instituted at a mean age of 13 years ($SD=2.0$) and which was associated with menarche at a mean age of 14.8 years ($SD=2.6$). 10.4% of participants had a severe hearing impairment and 4.2% had a severe visual impairment. Girls of school age were usually in mainstream school 93% ($N=94$); of these, 42% received additional educational support and 3% were in a special unit. The remaining 7% attended a special needs school.

Mental health

The prevalence of mental health and neurodevelopmental disorders was assessed using the DAWBA parental interview. 34% of participants met diagnostic criteria for at least one mental health disorder of clinical significance, a relative risk 2.6 times greater than typically developing girls (Table 1). 13% met criteria for an anxiety disorder and 1% met criteria for depression. None of the participants met criteria for a behavioural disorder. The proportion of participants with neurodevelopmental disorders was substantially higher than would be expected compared to female population norms. In the TS group, 13% met criteria for ADHD and 23% of participants met diagnostic criteria for an ASD. This is equivalent to a relative risk (RR) of 21.6 for ADHD and 57.5 for ASD compared to typically developing girls.

Of those with a mental health disorder ($n=34$), 59% had more than one type of disorder ($n=20$) and 40% had two or more types of disorder ($n=14$; Figure 1). Girls who met criteria for an ASD were at an increased risk in comparison to others with TS of both an associated emotional disorder (RR 2.9) and ADHD (RR 7.5; Table 2).

Autistic traits and friendships

The SRS-2 measures several domains of autistic behaviour and provides an overall likelihood score (Table 2). Only 39% of TS participants scored in the 'normal' range. 32.6% scored in the 'mild' and 'moderate' ranges and 28% scored in the 'severe' range, which indicates a strong probability of a clinical diagnoses of an ASD. Overall, nearly two-thirds (61%) had autistic-like characteristics in their social interactions by parental report (Table 2). The SRS-2 scores from teachers were similar to those provided by parents (Table 2).

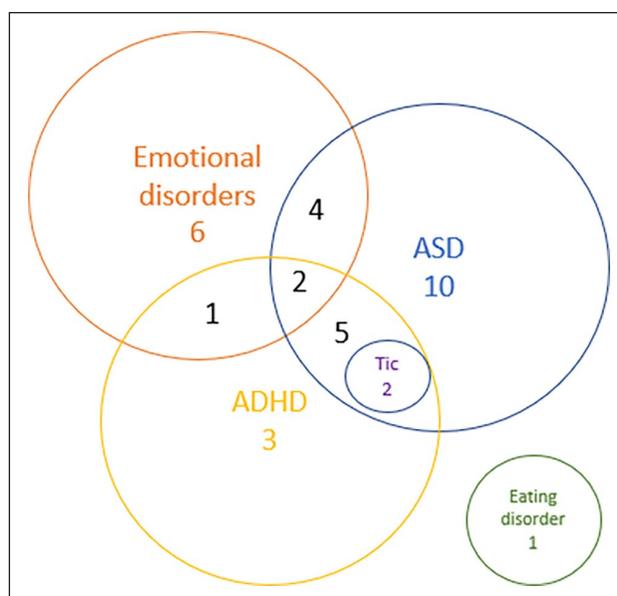


Figure 1. Venn diagram of co-occurring mental health and neurodevelopmental disorders in those meeting DSM-5 diagnostic criteria on the DAWBA.

On the SDQ 'peer interaction difficulties' scale parents reported that 68.7% of girls were scoring outside of the normal range compared to population norms, but ratings by teachers and the young women themselves differed (Table 3). Just 28.6% of teachers, and 25% of adolescents themselves, reported significant peer interaction difficulties.

The DAWBA autism module contains questions about friendships. According to parental report, children and adolescents with TS had more difficulties keeping friends than making friends compared to their typically developing peers. 71.6% of parents considered their daughter found it harder than average to make friends, whereas in the general population, the comparable figure is just 9.1%. 55.7% reported their daughter had difficulty keeping friends, compared to 5% of parents in the general population. Overall, 17% were considered to have no friends with whom they regularly spent time, compared with just 1.2% of typically developing girls (Table 3, Supplemental Table S2).

Discussion

This investigation is the largest to have been conducted into the mental health of young people with TS, using standardized instruments. We found that they experienced higher rates of psychiatric and social skills difficulties than age-matched girls from the general population. A third of participants met criteria for a mental health disorder; rates of neurodevelopmental disorders, anxiety, eating disorders and tic disorders were high relative to national data. The prevalence of depression was lower than in comparison girls from the general population at all ages (relative risk 0.35),

Table 2. SRS-2 scores by informant (5–19 years).

SRS-2 total score	TS Parent N= 104	TS Teacher N=26	TD Parent N= 1,896
Normal	39.4%	42.3%	84.1%
Mild	16.3%	26.9%	9.2%
Moderate	16.3%	7.7%	6.1%
Severe	27.9%	23.1%	0.6%
SRS-2 Scales, M (SD)	TS Parent N= 104	TS Teacher N= 26	
Social awareness	62.8 (14.0)	58.9 (13.9)	
Social cognition	63.4 (16.3)	58.0 (13.7)	
Social communication	64.4 (15.1)	61.1 (12.7)	
Social motivation	62.4 (13.8)	59.1 (12.2)	
Restricted interests and repetitive behaviour	67.2 (15.7)	67.9 (21.7)	
Total score	66.0 (15.2)	62.4 (14.3)	

SRS: Social Responsiveness Scale; TS: Turner Syndrome; TD: Typically Developing.

Table 3. DAWBA social communication and friendship data: Friendship and peer difficulties in TS.

Instrument	TS Parent	TD Parent	TS Teacher	TS Self-report
SDQ Peer difficulties scale, %	N=96 5 to 16 years	N=5,145 5 to 16 years	N=30 5 to 19 years	N=33 5 to 19 years
Normal	31.3%	79.8%	71.4%	75%
Slightly raised	8.3%	10.1%	10.7%	20.9%
High–very high	60.4%	10.1%	17.9%	4.1%
DAWBA Friendship, %	N=88 5 to 19 years	N=3,798 5 to 16 years		
How easy does your daughter find it to make friends?				
Harder than average	71.6%	9.1%		
About average	20.5%	35.1%		
Easier than average	8%	55.8%		
How easy does your daughter find it to keep friends?				
Harder than average	55.7%	5%		
About average	40.9%	35.7%		
Easier than average	3.4%	59.3%		
How many friends does she fairly often spend time with?				
None	17%	1.2%		
One	18.2%	4.2%		
Two to four	64.8%	43%		
Five to nine	0	40.3%		
10 or more	0	11%		

TS: Turner Syndrome; TD: Typically Developing; SDQ: Strength and Difficulties Questionnaire; DAWBA: Development and Wellbeing Assessment.

consistent with previous reports of TS-related depression in childhood and adolescence.^{16,20,21}

Parental reports obtained from the DAWBA and the SRS-2 indicated that approximately one in five girls met criteria for an ASD. This is equivalent to a 57-fold relative risk of meeting criteria for an ASD in TS compared to typically developing girls. There is undoubtedly a strong association between TS and risk of ASD, despite earlier claims to the contrary.² Most participants (61%) were

reported to have mild to moderate autistic traits, which had a clinically significant impact on their day-to-day social interaction. The SRS-2 profile was consistent with previous research using the SRS-1 on a smaller sample of girls with TS.⁹ TS girls who met criteria for ASD were also more likely to meet criteria for anxiety and/or ADHD. This is consistent with previous reports of co-occurring conditions in girls and young women with ASD without intellectual disabilities.^{40,41}

By parental report nearly three-quarters (71.6%) did not make friends easily and most had fewer friends than typically developing female peers. An important observation, consistent with previous reports, is that young people with TS did not themselves report any peer difficulties. Teachers also reported fewer peer interaction difficulties than parents. This is consistent with the observation that young women with ASD but normal-range intelligence are often overlooked in the classroom, because they do not cause any problems but tend to be withdrawn. Subtle social communication issues with peers can be difficult to detect in a classroom setting. There are a number of possible explanations for the discrepancy between young people and parent's accounts of socialization. We have consistently found a strong social-desirability bias in self-reports of social behaviour, during the course of previous TS investigations together with a lack of social insight. We assume these young people are reporting their desired rather than their actual experience of socialization,⁴² although there is an additional possibility that they are satisfied with fewer friendships than typical females of similar age.

Despite the genetic heterogeneity of karyotypes of participants in our study (monosomy, ring, partial deletion, etc.), the social communication phenotype was remarkably homogeneous. A number of different genomic theories have been proposed to account for the social skills difficulties and high rates of ASD in this condition. For instance, in typical females the second X-chromosome could act as a protective factor⁴³ increasing the threshold at which autistic traits are expressed. However, most sex chromosome aneuploidies are associated with an increased prevalence of ASD including 47,XYY syndrome (~19%–36% ASD), Klinefelter syndrome (XXY, ~11%–27% ASD), 48,XXYY syndrome (~28%–35% ASD), although possibly not in trisomy X syndrome.⁴ The risk of expressing autistic traits in TS could be influenced by an epigenetic imprinting effect.⁴⁴ Previous research has indicated that X-monosomic TS girls those whose single X was inherited from their mothers (~80%, X_m)⁴⁵ had more severe social communication difficulties than those who had inherited their X from their fathers (X_p). We did not have any information on the parental origin of the intact X-chromosome in this sample. Recent research from observation paradigms in social gaze impairments¹⁰ and from neuroimaging studies on brain development trajectories⁴⁶ support imprinting effects, as do studies of X-monosomic mice.⁴⁷

Strengths and limitations

Previous equivalent studies have not only been smaller in scale but were also less comprehensive in scope than this investigation. They focused exclusively on adolescents¹⁶ (n=122), or adult women¹⁷ (n=100) and did not discuss the neurodevelopmental characteristics of TS. A limitation of this investigation is that we did not have the opportunity to meet our participants face to face, to make our own

observations, but we relied largely upon online parental reports. The interview we employed, the DAWBA, is not a clinical diagnostic assessment. Formal psychiatric diagnoses require face-to-face clinical interviews and observations. Although it is possible that the rates of TS have been inflated, this is unlikely as the ASD module has been validated against multidisciplinary face-to-face clinical assessment³³ and was used in three national studies of children's mental health in the United Kingdom. Furthermore, the DAWBA is a more conservative measure of autism than the SRS-2. Only 54% of participants with scores in the severe range on the SRS-2 obtained a diagnosis of autism on the DAWBA ($\kappa=0.21, p < .001$).

Future studies will need to include child and adolescents self-reports, as well as investigate the discrepancies between them. Our study used normative data rather than recruiting a control participants. Future studies would benefit from recruiting participants matched for adaptive function and processing speed ability, as this is known to be different in TS. This study, like all studies of rare genetic disorders, may be affected by an ascertainment bias. Families needed to be engaged with their clinical services or the UK support society to find out about the study. It is also possible that the study adverts attracted more families who have children experiencing psychological difficulties than those without difficulties.

Conclusion

Taking a systematic approach to assessing mental health and neurodevelopment has revealed high rates of social skills difficulties, mental health disorders (anxiety disorders) and neurodevelopmental disorders (ASD and ADHD) in girls and young women with TS. The rates of co-occurring disorders were substantially higher in those that met criteria for an ASD. Clinicians managing the care of children with TS should consider referrals for ASD assessment, in order to facilitate the implementation of social skills support, as these have been shown to be effective in young women with TS.

Declarations

Ethics approval and consent to participate

Ethical approval for the SOAR study was obtained through the University College London Ethics Committee and the NHS West London Research Ethics Committee (UCL REC: 11837/001; IRAS: 219817). A written informed consent was obtained from all participants before enrolling in the study.

Consent for publication

Participants provided consent for use of their data in publication.

Author contribution(s)

Jeanne Wolstencroft: Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Writing – original draft; Writing – review & editing.

William Mandy: Conceptualization; Supervision; Writing – review & editing.

David Skuse: Conceptualization; Funding acquisition; Methodology; Project administration; Supervision; Writing – review & editing.

Acknowledgements

The authors thank the participants for making this work possible. The authors acknowledge Arlene Smyth at the Turner Syndrome Support Society, Dr Caroline Brain, Professor Gerard Conway and Dr Antoinette Cameron-Pimblett for their support of this project.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship and/or publication of this article: The SOAR study was funded by the Child Health Research CIO Studentship. Research conducted at the CRF UCL GOS ICH was supported by the NIHR.

Competing interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Availability of data and materials

The anonymous data used and analysed in this study is available from the corresponding author upon reasonable request.

ORCID iD

Jeanne Wolstencroft  <https://orcid.org/0000-0001-6160-9731>

Supplemental material

Supplemental material for this article is available online.

References

- Jacobs P, Dalton P, James R, et al. Turner syndrome: a cytogenetic and molecular study. *Ann Hum Genet* 1997; 61(Pt. 6): 471–483.
- Gravholt CH, Andersen NH, Conway GS, et al. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. *Eur J Endocrinol* 2017; 177(3): G1–G70.
- Sandberg DE, Singer D, Bugajski B, et al. Research priorities of people living with Turner syndrome. *Am J Med Genet C Semin Med Genet* 2019; 181(1): 43–51.
- Printzlau F, Wolstencroft J and Skuse DH. Cognitive, behavioral, and neural consequences of sex chromosome aneuploidy. *J Neurosci Res* 2017; 95: 311–319.
- Wolstencroft J, Mandy W and Skuse D. Experiences of social interaction in young women with Turner syndrome: a qualitative study. *Child: Care Health Develop* 2019; 46: 46–55.
- Creswell CS and Skuse DH. Autism in association with Turner syndrome: genetic implications for male vulnerability to pervasive developmental disorders. *Neurocase* 1999; 5: 511–518.
- Björlin Avdic H, Butwicka A, Nordenström A, et al. Neurodevelopmental and psychiatric disorders in females with Turner syndrome: a population-based study. *J Neuro-develop Dis* 2021; 13: 1–19.
- Lepage JF, Dunkin B, Hong DS, et al. Impact of cognitive profile on social functioning in prepubescent females with Turner syndrome. *Child Neuropsychol* 2013; 19(2): 161–172.
- Hong DS, Dunkin B and Reiss AL. Psychosocial functioning and social cognitive processing in girls with Turner syndrome. *J Dev Behav Pediatr* 2011; 32(7): 512–520.
- Hall SS, Riley MJ, Weston RN, et al. Effects of X chromosome monosomy and genomic imprinting on observational markers of social anxiety in prepubertal girls with Turner syndrome. *J Autism Dev Disord* 2022; 52(1): 16–27.
- Saad K, Abdelrahman AA, Abdel-Raheem YF, et al. Turner syndrome: review of clinical, neuropsychiatric, and EEG status: an experience of tertiary center. *Acta Neurol Belg* 2014; 114(1): 1–9.
- Kesler SR. Turner syndrome. *Child Adolesc Psychiatry Clin North Am* 2007; 16: 709–722.
- Lai MC and Baron-Cohen S. Identifying the lost generation of adults with autism spectrum conditions. *Lancet Psychiatry* 2015; 2(11): 1013–1027.
- Volkmar FR. Editorial: the importance of early intervention. *J Autism Dev Disord* 2014; 44(12): 2979–2980.
- Elder JH, Kreider CM, Brasher SN, et al. Clinical impact of early diagnosis of autism on the prognosis and parent-child relationships. *Psychol Res Behav Manag* 2017; 10: 283–292.
- McCauley E, Feuillan P, Kushner H, et al. Psychosocial development in adolescents with Turner syndrome. *J Dev Behav Pediatr* 2001; 22(6): 360–365.
- Cardoso G, Daly R, Haq NA, et al. Current and lifetime psychiatric illness in women with Turner syndrome. *Gynecol Endocrinol* 2004; 19(6): 313–319.
- Russell HF, Wallis D, Mazzocco MM, et al. Increased prevalence of ADHD in Turner syndrome with no evidence of imprinting effects. *J Pediatr Psychol* 2006; 31(9): 945–955.
- Green T, Bade Shrestha S, Chromik LC, et al. Elucidating X chromosome influences on Attention Deficit Hyperactivity Disorder and executive function. *J Psychiatry Res* 2015; 68: 217–225.
- Kiliç BG, Ergür AT and Öcal G. Depression, levels of anxiety and self-concept in girls with Turner's syndrome. *J Pediatr Endocrinol Metab* 2005; 18(11): 1111–1117.
- Rickert VI, Hased SJ, Hendon AE, et al. The effects of peer ridicule on depression and selfimage among adolescent females with Turner syndrome. *J Adolesc Health* 1996; 19(1): 34–38.
- Schmidt PJ, Cardoso GMP, Ross JL, et al. Shyness, social anxiety, and impaired self-esteem in Turner syndrome and premature ovarian failure. *JAMA* 2006; 295: 1373.
- Lesniak-Karpiak K, Mazzocco MMM and Ross JL. Behavioral assessment of social anxiety in females with Turner or Fragile X syndrome. *Journal of Autism and Developmental Disorders* 2003; 33: 55–67.
- Lepage JF, Clouchoux C, Lassonde M, et al. Cortical thickness correlates of socioemotional difficulties in adults with Turner syndrome. *Psychoneuroendocrinology* 2014; 44: 30–34.

25. Ford T, Goodman R and Meltzer H. The British Child and Adolescent Mental Health Survey 1999: the prevalence of DSM-IV disorders. *J Am Acad Child Adolesc Psychiatry* 2003; 42(10): 1203–1211.
26. Green H, McGinnity Á, Meltzer H, et al. Mental health of children and young people in Great Britain 2004, 2004. <https://digital.nhs.uk/data-and-information/publications/statistical/mental-health-of-children-and-young-people-in-england/mental-health-of-children-and-young-people-in-great-britain-2004>
27. Heiervang E, Stormark KM, Lundervold AJ, et al. Psychiatric disorders in Norwegian 8- to 10-year-olds: an epidemiological survey of prevalence, risk factors, and service use. *J Am Acad Child Adolesc Psychiatry* 2007; 46(4): 438–447.
28. Emerson E and Hatton C. Mental health of children and adolescents with intellectual disabilities in Britain. *Br J Psychiatry* 2007; 191: 493–499.
29. Office for National Statistics. Social and Vital Statistics Division, Office for National Statistics. Health and Care Division, Ford T and Goodman R. Mental Health of Children and Young People in Great Britain, 2004, 2005. [data collection]. UK Data Service. SN: 5269, DOI: 10.5255/UKDA-SN-5269-1. <https://beta.ukdataservice.ac.uk/datacatalogue/doi/?id=5269#!#1>
30. Office for National Statistics. Mental health of children and young people in England, 2017 [PAS], NHS Digital, <https://digital.nhs.uk/data-and-information/publications/statistical/mental-health-of-children-and-young-people-in-england/2017/2017> (2018, accessed 31 July 2019).
31. Fleitlich-Bilyk B and Goodman R. Prevalence of child and adolescent psychiatric disorders in Southeast Brazil. *J Am Acad Child Adolesc Psychiatry* 2004; 43(6): 727–734.
32. Aebi M, Kuhn C, Metzke CW, et al. The use of the development and well-being assessment (DAWBA) in clinical practice: a randomized trial. *Eur Child Adolesc Psychiatry* 2012; 21(10): 559–567.
33. Coscini N, Srinivasan R and Skuse D. Validating the developmental and well-being assessment (DAWBA) in a clinical population with high-functioning autism. *1000Res* 2020; 9: 622.
34. Wolstencroft J, Wicks F, Erwood M, et al. Neuropsychiatric risk in children with intellectual disability of genetic origin: IMAGINE – the UK national cohort study. *SSRN Electr J*, [https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366\(22\)00207-3/fulltext](https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(22)00207-3/fulltext)
35. Goodman A, Lamping DL and Ploubidis GB. When to use broader internalising and externalising subscales instead of the hypothesised five subscales on the Strengths and Difficulties Questionnaire (SDQ): data from British parents, teachers and children. *J Abnorm Child Psychol* 2010; 38(8): 1179–1191.
36. Bölte S, Westerwald E, Holtmann M, et al. Autistic traits and autism spectrum disorders: the clinical validity of two measures presuming a continuum of social communication skills. *J Autism Dev Disord* 2011; 41(1): 66–72.
37. Amundson E, Boman UW, Barrenäs M-L, et al. Social Responsiveness Scale, (SRS-2) (Western Psychological Services, Torrance, CA). *J Autism Dev Disord* 2012; 19: 629–634.
38. Constantino JN and Christian PG. Social responsiveness scale: SRS-2. Torrance, CA: Western psychological services, 2012. <https://www.wpspublish.com/srs-2-social-responsiveness-scale-second-edition>
39. Office National Statistics. English indices of deprivation 2015: GOV.UK. GOV.UK. <https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015> (2015, accessed 5 December 2018).
40. Margari L, Palumbi R, Pescechera A, et al. Sex-gender comparisons in comorbidities of children and adolescents with high-functioning autism spectrum disorder. *Front Psychiatry* 2019; 10: 159.
41. de Giambattista C, Ventura P, Trerotoli P, et al. Sex differences in autism spectrum disorder: focus on high functioning children and adolescents. *Front Psychiatry* 2021; 12: 539835.
42. Bauminger N and Kasari C. Loneliness and friendship in high-functioning children with autism. *Child Dev* 2000; 71(2): 447–456.
43. Werling DM and Geschwind DH. Sex differences in autism spectrum disorders. *Curr Opin Neurol* 2013; 26: 146–153.
44. Skuse DH, James RS, Bishop DVM, et al. Evidence from Turner's syndrome of an imprinted X-linked locus affecting cognitive function. *Nature* 1997; 387: 705–708.
45. Sagi L, Zuckerman-Levin N, Gawlik A, et al. Clinical significance of the parental origin of the X chromosome in Turner syndrome. *J Clin Endocrinol Metab* 2007; 92(3): 846–852.
46. O'Donoghue S, Green T, Ross JL, et al. Brain development in school-age and adolescent girls: effects of Turner syndrome, estrogen therapy, and genomic imprinting. *Biol Psychiatry* 2020; 87: 113–122.
47. Davies W, Isles A, Smith R, et al. Xlr3b is a new imprinted candidate for X-linked parent-of-origin effects on cognitive function in mice. *Nat Genet* 2005; 37: 625–629.