

## **Mental health and behavioural problems in children with XYY: a comparison with intellectual disabilities**

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### **ABSTRACT**

**Background:** The phenotype of children with XYY has predominantly been defined by comparison to other sex chromosome aneuploidies (SCA) trisomies affecting males; however, the intellectual ability of children with XYY is lower than children with other SCA trisomies. It is not known to what extent the phenotype identified to date is specific to XYY, rather than a reflection of lower IQ. This study evaluates the mental health and behaviour of children with XYY, in comparison to children with intellectual disabilities of heterogeneous genetic origin.

**Methods:** 15 children with XYY and 30 controls matched for age (4-14 years), sex and intellectual ability were ascertained from the IMAGINE ID study. IMAGINE ID participants have intellectual disabilities due to genetic anomalies confirmed by NHS Regional Genetic Centre laboratories. The mental health and behaviour of participants was examined with the Development and Wellbeing Assessment and the Strengths and Difficulties Questionnaire.

**Results:** Children with XYY experienced significantly more frequent and intense temper outbursts than the control group.

**Conclusion:** Our results suggest that temper outbursts may be specifically associated with the XYY phenotype. These problems have a significant impact on the daily lives of boys with XYY and their families. It is crucial to ensure that families are well supported to manage these difficulties.

## INTRODUCTION

XXYY is a rare genetic sex chromosome aneuploidy (SCA) which is associated with intellectual disabilities (ID). It is caused by a double nondisjunction during meiosis, resulting in the affected individual inheriting two additional sex chromosomes. The syndrome affects 1 in 18,000 to 40,000 males (Sorensen et al., 1978) and over two-thirds of diagnoses are made by genetic testing obtained following evaluation for developmental delays or behavioural difficulties (Tartaglia et al., 2008). XXYY is also associated with a distinct physical phenotype and range of medical problems (Box 1).

Developmental delay is common in XXYY; over 90% of children present with speech and language delay and over 75% have motor development delay in early childhood (Tartaglia et al., 2008). Nearly all children with XXYY require special education for learning disabilities and language difficulties, which can persist into adulthood (Tartaglia et al., 2008).

The intellectual ability of individuals with XXYY varies significantly (Tartaglia et al., 2008). The majority of XXYY adults score within the borderline (IQ 70–79) to intellectually disabled (IQ < 70) range on full scale IQ tests (Borgaonkar et al., 1970, Visootsak and Graham, 2009, Tartaglia et al., 2008). As in many other SCAs (eg. XYY, XXY) visuo-spatial IQ is a relative strength compared to verbal IQ. More recent findings also indicate that verbal IQ is lower in adults than in children, whereas there are no significant differences in visuo-spatial IQ (Tartaglia et al., 2008).

XXYY is linked to an increased risk of mental health disorders; most notably Attention Deficit Hyperactivity Disorder (ADHD) which is reported in nearly three out of four patients (Tartaglia et al., 2008, Tartaglia et al., 2012); Autism Spectrum Disorder (ASD) which is reported in up to half of cases (Tartaglia et al., 2017) and behavioural problems such as impulsivity, aggression and mood instability (Tartaglia et al., 2008, Tartaglia et al., 2012). Many studies report broad difficulties with social skills (Tartaglia et al., 2008) (Visootsak and Graham, 2009, Cordeiro et al., 2012). Cordeiro (2012) found that 37.5% of XXYY children had a prior diagnosis of ASD and 43.8% had severe scores on a measure of autistic traits (the Social Responsiveness Scale, SRS). Whilst analysis of the SRS subscales showed significant difficulties in all areas, scores on the social motivation subscale were only just outside the normal range, suggesting that social motivation is the least impaired domain (Cordeiro et al., 2012). There was a significant, but weak correlation between verbal abilities and SRS scores and the authors suggest that poor language skills may contribute to social difficulties in children with XXYY.

Anxiety and depression are common and affect about half of individuals with XXYY by adulthood (Tartaglia et al., 2008, Tartaglia et al., 2012). In a small study of children (n=24), 46% were found to meet criteria for a diagnosis of oppositional defiant disorder (ODD) (Tartaglia et al., 2006), but in a larger study including children and adults (age range: 6-55), 10% were diagnosed with ODD (Tartaglia et al., 2008). Individuals with XXYY have been found to have more problems with hyperactivity, aggression and conduct than those with XXY (Tartaglia et al., 2006, Tartaglia et al., 2008) and these symptoms were not associated with IQ. The prevalence and characteristics of eating and sleeping difficulties have not been systematically reviewed, but sleep disturbances, feeding difficulties and sugar cravings have been commonly reported by parents (Tartaglia et al., 2008).

To date the XXYY phenotype has predominantly been defined by comparison to other SCAs affecting males (Ref + Visootsak et al., 2007), without being matched for intellectual ability. Children with XXYY have a lower intellectual ability than those with XYY and XXY, but a higher ability than those with XXXYY and XXXXY (Printzlau et al., 2017). It is not known to what extent the phenotype identified thus far is specific to XXYY, rather than a reflection of their intellectual ability. Children with ID are more likely to have psychiatric diagnoses than children without ID; a national survey that compared the wellbeing of children with and without an ID showed that 39% of those with ID had psychiatric disorders compared to 8.1% of those without ID (Emerson, 2003).

XXYY is typically identified due to concerns about the associated developmental delay. Given the rarity of the condition, most children will be managed in non-specialist settings that manage children with ID of all causes. The clinical phenotype of XXYY therefore needs to be further differentiated from that of ID in general, in order to ensure that the specific needs of children with XXYY are met within such non-specialist settings.

This study aims to compare the phenotypes of children with XXYY to matched controls that have an equivalent level of ID, of known genetic origin. We investigate the extent to which the XXYY phenotype is distinct.

## **METHODS**

### **Data Source**

Data were obtained from the IMAGINE ID project. This is a large multicentre Medical Research Council and Medical Research Foundation funded study of psychiatric risk and developmental delay in children with genetic disorders.

The IMAGINE ID cohort comprises children with developmental delay due to a genetic anomaly. In the UK children with developmental delay undergo genetic testing by National Health Service (NHS) Regional Genetic Centres (RGCs) following an initial evaluation by paediatricians. Children who are found to have a genetic anomaly that contributes to developmental delay following genetic testing are recruited into IMAGINE ID via NHS RGCs or support groups including Unique ([www.rarechromo.co.uk](http://www.rarechromo.co.uk)) and XXYY UK ([www.xxyy.co.uk](http://www.xxyy.co.uk)). Genetic diagnosis was confirmed by RGCs for all participants including those recruited via parental support groups. The majority of participants in the IMAGINE ID study have been ascertained as having structural chromosomal anomalies, for example, pathogenic copy number variants (CNVs).

The IMAGINE ID sample is representative of the English population. This has been confirmed by analysis of UK Office for National Statistics 2011 census data. Index of Multiple Deprivation scores are available for the sample and are also representative of the English population. Detailed information on the cohort has been collected online via caregiver-report measures (see below). Ethical approval for the study was obtained from the London - Queen Square Research Ethics Committee.

### **Sample**

15 children with XXYY were identified. Two controls were then selected from the IMAGINE ID cohort for each XXYY case; this was to improve statistical power given the rarity of XXYY (Coggon et al., 2009). Controls were matched with cases for age, sex, parental estimates of mental age and language impairment. Controls were selected to be heterogeneous with regard to genetic condition (Table 1) in order to reduce bias caused by the over-representation of conditions which may reduce risk for emotional and behavioural problems.

### **Measures**

#### *The Development and Wellbeing Assessment (DAWBA)*

The DAWBA is a validated and widely used research instrument (Goodman et al., 2000, Goodman et al., 2011). It collects information on a wide range of behaviours and specific mental health difficulties and generates probability scores for DSM-IV diagnoses based on population norms which are then confirmed by a clinician. This study used the caregiver-report measure of the DAWBA which was administered online or by telephone. Respondents complete detailed sections which are

organised into modules. A background section that covers the child's general physical health, development, education and family was also administered. The DAWBA incorporates both structured and semi-structured items. Each module is comprised of screening questions, followed by questions regarding specific symptomatology and an estimate of functional impairment. This includes questions on parental estimates of mental age and language impairment. Questions pertaining to mental age from the DAWBA have been validated in a subset of the IMAGINE ID cohort by comparison with the Functional Academics Subscale of the Adaptive Behaviour Assessment Schedule, 2<sup>nd</sup> Edition (ABAS-II, parent form, 5-21 years). This showed high correlation between the two measures (Pearson correlation coefficient 0.74; 95% CI [0.64, 0.81])

#### *Strengths and Difficulties Questionnaire (SDQ)*

This study used a caregiver report version of the SDQ. The SDQ is a widely used and validated measure (Goodman, 2001, Goodman and Goodman, 2009, Bøe et al., 2014); it is a brief behavioural screening questionnaire that can be administered to the primary caregivers of 4-18 year olds. The SDQ scores have been validated in the general population. The SDQ covers common areas of emotional and behavioural difficulties as well as positive attributes; it can be divided into 5 subscales of 5 items each: emotional symptoms, conduct problems, hyperactivity-inattention, peer problems and prosocial behaviour. Each subscale is scored out of 10 and each item is scored according to a 3 point scale (0 = 'not true', 1 = 'somewhat true', and 2 = 'certainly true'). A total difficulties score (maximum score 40) can be calculated using the emotional problems, conduct problems, hyperactivity-inattention and peer problems subscales. The SDQ also includes an impact supplement which captures information on the parent's perception of the severity of their child's problems and reflects the impairment caused by their child's difficulties.

#### *Everyday Feelings Questionnaire (EFQ)*

The Everyday Feelings Questionnaire (EFQ) was administered to the parents of participants, who reported on themselves. The EFQ is a validated ten-item self-report measure of psychological distress and well-being which is designed to be used in non-clinical samples of adults (Uher and Goodman, 2010, Mann et al., 2013, Bøe et al., 2014). This was administered to parents to assess their wellbeing. The EFQ covers symptoms relating to anxiety and depression as well as items pertaining to psychological well-being such as optimism, self-esteem and coping. Respondents are asked to answer questions based on their experiences over the prior 4 weeks. Each item is scored according to a 5-point scale (none of the time, a little of the time, some of the time, most of the time, and all of the time). Scores between 0 and 12 are considered 'close to average', scores between 13 and 17 are 'slightly raised', scores between 18 and 22 are regarded as 'high' and those above 23 are 'very high'.

#### **Analysis**

Analyses were conducted using Stata 13. Fisher's exact or Chi-squared test and the Mann-Whitney U test were used to assess for difference between the two groups across a range of baseline variables as well as mental health and behavioural problems. Fisher's exact test was used in preference to the Chi-squared test when expected cell values were below 5. These were used in the analysis of the DAWBA data which are categorical. The Mann-Whitney U test was used for the SDQ data which are continuous. The Mann-Whitney U test was used as data were non-normally distributed.

## **RESULTS**

### **Baseline characteristics**

15 participants with XYY were identified and matched with 30 controls. The mean age of combined participant groups was 8.89 years (SD = 3.13, range 4-14 years) and the estimated developmental delay was 3.02 years (eg. 3 years behind peers, SD = 1.30, range 0-6 years). The mean estimated language delay was 2.95 years (SD = 1.26, range 1-7 years). There were no significant differences in age, estimated developmental delay or language delay between the two groups. No participants with XYY were receiving testosterone therapy at the time of completion of the assessments. Children with XYY of school age were more likely to be educated in special schools than controls (XYY 71%, Control 29%;  $p=0.02$ ). All participants lived in the UK or dependent territories. There were no differences in demographics or social deprivation between the two groups; however all children with XYY had been recruited into IMAGINE ID from the UK XYY society whereas control participants were more likely to have been recruited from NHS RGCs (XYY: 100% support group, Control: 67% support group, 33% RGC,  $p = 0.000$ ). For further information about the genetic disorders present in the control group please refer to Table 1.

### **Strengths and Difficulties Questionnaire**

There were significant differences between the two groups on the “total difficulties” score as well as the emotional and conduct problems subscales, to which the emotional and conduct subscales make the major contribution. The mean total difficulties score for both the XYY and control groups were classified as ‘very high’ according to the established SDQ norms (Table 2).

Further analysis of the conduct problems subscale showed significant differences between the two groups on three out of five items: children with XYY were more often reported as engaging in stealing (XYY 50%, Control 11%;  $p = 0.008$ ) and fighting (XYY 64%, Control 21%;  $p = 0.017$ ), and were less likely to be obedient (XYY 60%, Control 90%;  $p = 0.042$ ). There were no significant differences between both groups with regard to tantrums (XYY 93%, Control 77%;  $p= 0.24$ ) and lying (XYY 71%, Control 43%;  $p= 0.11$ ).

Further analysis of the emotional difficulties subscale suggested that boys with XYY were more likely to experience somatic symptoms of anxiety (XYY 87%, Control 43%;  $p = 0.045$ ). Although boys with XYY experienced high levels of other emotional symptoms there were no significant differences between groups on these items: unhappiness (XYY 67%, Control 43%;  $p = 0.07$ ), worrying (XYY 80%, Control 73%;  $p = 0.57$ ), clinginess (XYY 100%, Control 93%;  $p = 0.88$ ), and being afraid (XYY 100%, Control 80%;  $p = 0.66$ ).

### **Development and Wellbeing Assessment**

Analysis of DAWBA psychiatric diagnoses revealed that a higher proportion of the XYY group met criteria for oppositional defiant disorder (ODD) compared to controls (Table 3). A higher proportion of the XYY group met diagnostic criteria for social phobia, generalised anxiety, ADHD and tics than controls; however these results were not statistically significant. A lower proportion of children in the XYY group met criteria for specific phobia and ASD than controls; these results were not significant (Table 3). No participants in either group met criteria for major depression.

Children in the XYY group were reported as being more likely to display frequent significant temper outbursts (XYY 47%, Control 10%;  $p = 0.01$ ) and irritability (XYY 53%, Control 20%;  $p=0.03$ ). Review of free text responses from semi-structured components of the DAWBA revealed the intensity of the outbursts often experienced by children with XYY. They were reported to experience angry outbursts which could involve lashing out, throwing objects impulsively and engaging in destructive behaviour. Outbursts were emotionally distressing to the child and involve self-injurious behaviour

or threats to self-harm. These incidents could take place on a daily basis and were often perceived by caregivers to be unpredictable (Box 2).

Review of free text responses in the section of the DAWBA that inquired about eating behaviours identified that problematic sugar cravings were reported more often in the XXY group than controls (XXY 40%, Control 6%;  $p=0.01$ ). These were often described as being so intense that they were associated with stealing behaviours (Box 3).

Review of the strengths section of the DAWBA highlighted that children with XXY were generous (100%), lively (87%), caring (93%), affectionate (87%), grateful (80%), polite (93%), good fun (93%) and able to bounce back from setbacks (73%). They were also reported as getting on well with their family (100%) and as enjoying family activities (80%).

### **Everyday Feelings Questionnaire**

For both the XXY and control groups, caregiver EFQ scores fell into the 'slightly raised' range ( $M = 17.6$ ;  $SD = 6.7$ ; range: 4-34) based on the norms described above. There were no significant differences in EFQ scores between the two groups (XXY mean = 17.8,  $SD = 4.95$ ; Control mean = 17.4,  $SD = 7.54$ ;  $p = 0.68$ ).

## **DISCUSSION**

This is the first study to systematically assess the mental health and behaviour of children with XXY to controls matched for age as well as intellectual and language ability. Whilst previous reports have identified behavioural problems such as aggression, impulsivity and mood instability in children with XXY, this study is the first to include a detailed assessment of conduct problems alongside other psychopathology. The main differences between the XXY and control groups were a greater frequency and intensity of temper outbursts and irritability in children with XXY. These difficulties were not highlighted in our short behavioural screening questionnaire (the SDQ), as the level of conduct problems was high in both groups, however a detailed examination of the conduct of children with the DAWBA questionnaire revealed significant differences.

Our assessments have shown the substantial impact these conduct problems have on the daily lives of boys with XXY and their families. These findings support qualitative descriptions of behaviour, where boys are typically described as sweet and loving but also as easily frustrated and impulsive and prone to mood swings and temper outbursts (<http://www.rarechromo.co.uk/html/DisorderGuides.asp>).

Children with XXY are significantly more intellectually impaired than children with common SCAs (such as XXY, XYY, XXX or XO) (Visootsak and Graham, 2009). Children with ID are more likely to experience emotional and behavioural problems (Emerson, 2003, Emerson and Hatton, 2007). As a result, a comparison of XXY with other SCAs may have led to a misattribution of difficulties with social communication and attention/concentration to the XXY phenotype rather than their intellectual impairment. The results of this study indicate that temper outbursts are specifically associated with the XXY phenotype but that difficulties with social communication and attention/concentration may relate to intellectual impairment. This is in keeping with the findings of previous studies which found elevated rates of conduct problems in XXY in comparison to XYY (Davis et al., 2006, Tartaglia et al., 2006), but not in comparison to XXXY/XXXXY (Visootsak et al., 2007).

Comments from parents indicate that the intensity of the temper outbursts seen in XXY can be distressing for the child and their family (see Box 2). These difficulties have a substantial impact. It is

crucial to ensure that families are well supported to manage these difficulties. In the general population, children from socially disadvantaged areas have higher levels of conduct disorders (Bywater et al., 2009); however, conduct problems were present in the majority of the sample with XYY despite coming from diverse socio-economic backgrounds. This suggests that the causes of conduct problems in those with XYY may be different to the causes of conduct problems in the general population. Conduct problems in the general population have been associated with specific parenting styles (Brestan and Eyberg, 1998, Vostanis et al., 2006) which has led parents to be considered responsible for their child's difficulties. It is important that parents of children with conduct disorders are not stigmatised for their children's behaviour. For children with XYY these problems may, at least partially, be explained by them being a feature of the XYY behavioural phenotype. In addition, boys with XYY were noted to experience high levels of emotional difficulties, particularly somatic symptoms. It may be that their outbursts reflect anxiety and frustration that they are not able to verbalise.

Awareness of the higher levels of conduct problems in children with XYY indicates the need for more intensive behavioural support utilising specialist techniques, given that these problems may be related to the XYY behavioural phenotype. Anecdotally, parents report an increase in severity of behavioural outbursts at around the age of 8 to 9 years (Tartaglia et al., 2008), which incidentally is the mean age of our sample. It may be that the increased intensity of outbursts is linked to developmental changes occurring at this age. It would be important to investigate whether pre-existing interventions for conduct problems are effective in those with XYY; in particular, optimising the timing of intervention is crucial to better manage severe outbursts at 8 to 9 years. Improving the management of conduct problems in children with XYY may also mean that they could be supported to remain in mainstream educational settings; this requires further investigation.

Whilst information from our participants suggested that children and families with XYY receive support from a range of services (including specialist education, paediatrics, educational psychology, speech and language therapy, occupational therapy, social care and mental health), the nature of the specific interventions being offered was not clear. Evidence based parenting interventions such as the Incredible Years/Triple P (Bywater et al., 2009) or conceptualisation of outbursts with the well-established ABC behavioural model (Ellis, 1991) may be useful in understanding the triggers for such behaviours and in developing a suitable management strategy.

Longitudinal studies of conduct problems in children with XYY would be beneficial to determine the developmental trajectory of these problems across the lifespan. Epidemiological study of conduct problems has identified different developmental subtypes. In childhood, two subtypes with distinct longer term outcomes have been delineated; the life course persistent subtype and the childhood limited subtype (Odgers et al., 2007). The life course persistent subtype is associated with poor longer term outcomes including mental health, physical health, victimisation and offending behaviour, whereas the outcomes of those with the childhood limited conduct problems are similar to those with low levels of conduct problems in childhood. Indeed, within the IMAGINE ID cohort, there are 5 adults with XYY syndrome, none of whom appear to have significant difficulties with such behaviour. This highlights the importance of a developmental approach to the presentation of these difficulties.

In other SCAs such as Turner Syndrome, problems with attention and concentration are significant in childhood, but resolve during adolescence without intervention (Skuse, 2009). Some behaviours follow a specific developmental course in SCAs, which may be linked to the genetic anomaly. Understanding the developmental trajectory of conduct problems in XYY will provide important prognostic information that will be valuable for both clinicians and families.

Previous studies in XYY have identified a relative preservation in social motivation (Cordeiro et al., 2012). In our sample social motivation in children with XYY was not explored in detail, but participants were described as being caring, affectionate and generous in the strengths section of the assessment, reflecting their interest in others. This warrants further investigation as the interest in social interaction may be utilised in developing interventions. In addition, it may be that preservation of social motivation as well as relative weakness of language skills predisposes children with XYY to emotional distress and outbursts as well as subsequent guilt and remorse (Box 2). This may in turn lead to low self-esteem and increase vulnerability to future mental health problems. Therefore a focus on improving self-esteem or resilience may be of benefit. An increased desire to 'fit in' may mean that children with XYY are more susceptible to negative peer influences i.e. encouragement by peers to engage in problematic behaviour.

Children with XYY were more likely to be educated in a specialist setting than controls. Based upon previous research findings, this might have been attributed to intellectual impairment and language difficulties, but this is not the case in our sample given that we matched for age and cognitive ability. It would be interesting to explore whether the differences in educational setting are due to higher levels of conduct problems in children with XYY, which are more difficult to manage in mainstream educational settings. However, this may mean that the social and educational advantages that mainstream education may confer (Education and Skills, 2004) (EDUCATION, 2004) are lost. Despite reports of higher levels of conduct problems in children with XYY, there were no differences in caregiver accounts of their own emotional wellbeing which is encouraging.

Previous studies have found high rates of ASD and ADHD in those with XYY. Our study confirmed this finding; however, there were no significant differences in social communication or attention/activity problems. This suggests that the higher rates of these disorders in children with XYY may be linked to their intellectual and language impairment rather than being a specific feature of XYY. However it is important to note the high levels of ASD and ADHD diagnoses in our control group, which comprised children who were ascertained by NHS RGCs as a result of a confirmed diagnosis of ID of known genetic origin. The majority of participants in the control group had been ascertained as having pathogenic copy number variants (CNVs) that were the cause of their developmental difficulties. Over 50% of our control group met criteria for ASD and 46% met criteria for ADHD, whereas national UK studies using the DAWBA have reported point prevalences of ASD in 8% and ADHD in 8.3% of children with ID (Emerson and Hatton, 2007). The discrepancy between IMAGINE ID and previous national surveys of children with ID could simply be related to different modes of ascertainment. But it is more likely that the genetic origin of the ID influences the range, severity and complexity of difficulties within the IMAGINE ID cohort. It is possible that ID related to common polygenic variation is less likely to predispose individuals to mental health and behavioural problems than pathogenic variants. As such, it will also be important to compare children with XYY to children with ID of other causes, in order to fully delineate the mental health and behavioural phenotype.

None of the children with XYY in our study were receiving testosterone replacement therapy at the time of participation. Endocrine evaluation for testosterone therapy should commence in early adolescence. Testosterone therapy has beneficial effects on physical health (Tartaglia et al., 2008). However, the effect of testosterone therapy on mental health and behaviour has not been clear until more recently (Tartaglia et al., 2008, Tartaglia et al., 2011, Heuser et al., 1999, Sourial and Fenton, 1988, Lee, 1996). Overall, testosterone therapy appears to have a positive effect on conduct, behaviour and aggression, but should be monitored carefully in patients with mental health problems such as bipolar or psychiatric disorders due to a previous case report suggesting possible increased aggression in an individual with schizophrenia (Lee et al., 1996). There has previously been debate in the literature regarding the optimal timing of testosterone therapy and its association with

behavioural problems in XYY (Tartaglia et al., 2008, Heuser et al., 1999, Sourial and Fenton, 1988, Lee, 1996). This suggests that the conduct problems arise prior to testosterone therapy. It is unclear whether testosterone therapy would exacerbate pre-existing conduct problems; this would benefit from further research.

Consistent with previous anecdotal reports, noticeable sugar craving in children with XYY was also reported by caregivers in our study (see box 3). This would benefit from further exploration as XYY has been associated with dental problems and peripheral vascular disease (Tartaglia et al., 2008).

### **Strengths and Limitations**

The strengths of this study are that it is the first research to explore the XYY phenotype in relation to those with ID of genetic origin who have been matched for language ability and developmental delay. The sample consists entirely of children, whereas previous studies have been made up of both children and adults. It is important to delineate presentation according to age, as the symptoms of psychopathology can manifest themselves differently across the lifespan. It is one of the few studies to have simultaneously assessed a broad range of behaviours and mental health symptoms, rather than historical diagnoses. Due to the overlap in symptomatology between psychiatric diagnoses, collecting information of such depth and breadth improves diagnostic accuracy. For example, impulsive behaviour may be observed in children with conduct problems and/or ADHD; in order to avoid misattribution, both of these areas need to be assessed. The children in our cohort come from a nationally representative mix of urban and rural areas across the UK, so the results are generalisable to the UK and Europe.

XYY is a rare condition; it is one of the rarest SCAs and our study only examined behaviour in children. This limits the sample size and the power of the study. In addition, our participants were recruited from a support group which introduces recruitment bias as participants recruited via support groups may be different from those recruited via other pathways. XYY is a heterogeneous condition; therefore our participants may represent a more extreme developmental phenotype limited to childhood. It is important that the results of this study are interpreted in a developmental context, in light of the heterogeneity of XYY and the recruitment bias of this study.

No objective assessments of cognition or adaptive function were performed and the study relied on parental report. However, families recruited into the IMAGINE ID cohort were genetically tested by NHS RGCs as result of a confirmed diagnosis of ID. In addition, comparison of the DAWBA mental age questions with the ABAS functional academic subscale shows good correlation in a subset of the IMAGINE ID cohort. Our measures of behaviour were also based on caregiver reports, which may introduce bias into the study but there are few reliable and valid assessments of mental health and behaviour for children with ID. Young children (4-10), let alone children with ID, are not reliable informants on their own behaviour and mental health. Future studies should consider multiple caregiver and teacher reports to triangulate information. The study design is cross-sectional; further longitudinal studies would be of benefit in order to further delineate the XYY mental health and behavioural phenotype across the lifespan.

### **Implications and Future Research**

Our results have important implications for clinical practice and intervention: whilst the prevalence of ASD, ADHD and anxiety in those with XYY is similar to those with ID of known genetic origin, the rates of conduct problems are higher. Knowledge of these difficulties with conduct problems may reduce the stigma associated with having a child with significant conduct problems, which are often attributed to parenting practices. It is helpful to raise awareness that these conduct problems may be a feature of the XYY phenotype, rather than simply attributing them to the 'naughty child' stereotype.

Future research in this field should focus on understanding the developmental course of conduct problems in XYY and compare the nature of the difficulties in XYY with ID of non-genetic causes. At present, the developmental trajectory of conduct problems in XYY is not clear and there is no way to determine whether children with XYY are more likely to fall into the childhood limited or the life course persistent trajectory (Odgers et al., 2007). Should they fall in the childhood limited trajectory, this would be important prognostic information that would be reassuring for parents. At present we must work based on evidence from the general literature on conduct problems. We know that the children with conduct problems at highest risk of poor long-term outcomes are those with additional family risk factors (e.g. socio-economic status, childhood adversity etc.)(Loeber et al., 2000, Burke et al., 2002). The most intensive interventions should be targeted at children with XYY with these risk factors until the trajectories are fully understood.

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