Major Research Project

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An Exploration of the Experiences of Children and Young People with 22q11.2 Deletion Syndrome

Section A: Neurodevelopmental Trajectories and Social & Educational Outcomes for Children and Young People with 22q11.2 Deletion Syndrome: A Systematic Review
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Section B: A Grounded Theory Exploration of the Experiences of Children and Young People with 22q11.2 Deletion Syndrome, Building a Model of Stressors and Coping Strategies
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Summary of the Project

This project relates to the experiences of children and young people with 22q11.2 deletion syndrome. 22q11.2 deletion syndrome is a complex and highly variable genetic syndrome characterised by multiple complex physical abnormalities and a neurodevelopmental phenotype that can impact on several domains of the young person's life, including social and educational functioning.

Section A comprised a systematic review and quality assessment of the longitudinal literature relating to neurodevelopmental trajectories to understand the impact of neurodevelopment on social and educational outcomes for children and young people with 22q11.2 deletion syndrome. The longitudinal evidence relating to several domains of neurodevelopment, including cognitive development, language development, executive functioning development and the presence of neurodevelopmental conditions such as ASD and ADHD, and associations between these measures and social and educational outcomes, were reviewed. Limitations and directions for future research were discussed.

Section B comprised a qualitative, modified grounded theory investigation of children and young people's experiences of stress and coping. Ten children and young people (aged 10-15) with 22q11.2 deletion syndrome took part in a semi-structured interview and through grounded theory analysis a theoretical model was developed with ten related categories. Resonance with existing theory and directions for future research were outlined.

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Section A

Neurodevelopmental Trajectories and Social & Educational Outcomes for Young People with 22q11.2 Deletion Syndrome: A Systematic Review

Word count: 7,524 (236)

Abstract

Background: 22q11.2 deletion syndrome is a complex and highly variable genetic syndrome characterised by multiple complex physical abnormalities and neurodevelopmental challenges affecting both social and educational outcomes for young people. **Method**: This study comprised a systematic review of the longitudinal literature relating to neurodevelopmental trajectories in children and young people with 22q11.2 deletion syndrome, and the impact of these trajectories on social and educational outcomes. Data was extracted from the included studies (N=9) and a quality appraisal and narrative analysis of key findings was produced. **Results:** The findings suggests that while cognitive and executive functioning abilities do not predict social outcomes in children and young people with 22q11.2 deletion syndrome, ADHD diagnosis may be predictive of social outcomes. In addition, both executive functioning and language abilities uniquely and independently predict educational outcomes in children and young people with 22q11.2 deletion syndrome. While executive functioning has been found to be predictive of school achievement in typically developing peers, current evidence indicates a stronger relationship between executive functioning and school achievement for children and young people with 22q11.2 deletion syndrome. **Conclusion:** Although equivocal, the evidence suggests that further investigation of different domains of neurodevelopment and their impact on social and educational outcomes would be valuable areas of enquiry. Limitations of the review and gaps in the existing research are discussed.

Keywords: 22q11.2 Deletion Syndrome, Children and Young People, Neurodevelopment, Social Outcomes, Educational Outcomes

Introduction

22q11.2 Deletion Syndrome

This review examines the literature relating to neurodevelopmental trajectories and social and educational outcomes for children and young people (CYP) with 22q11.2 deletion syndrome (22q11DS). 22q11DS is a copy number variant resulting in the loss of DNA on the long arm of chromosome 22. It is estimated to be present in 1 in 2,000-4,000 live births (Scrambler, 2000), although recent analysis suggests the syndrome could be more common than previously understood (Grati et al., 2015).

The syndrome is known to have a highly variable phenotypic expression. Common medical problems include congenital heart defects, immunodeficiency, hypothyroidism, scoliosis of the spine, and palatal problems impacting on feeding and speech (Bassett et al., 2011). However, there are over forty other possible physical anomalies which may be present with the syndrome (Goldberg et al., 1993). Individuals' experiences of the syndrome may range from the presence of multiple, life-threatening conditions to only one or two associated features (McDonald-McGinn & Sullivan, 2011).

In addition to medical features, there are neurodevelopmental components to the syndrome. The neurodevelopmental phenotype of 22q11DS is also highly variable, both during development and between individuals diagnosed with the syndrome. Features include an increased risk of developmental delay, cognitive difficulties, problems with executive functioning, and behavioural and psychiatric difficulties (De Smedt et al., 2007; McDonald-McGinn et al., 2015), with autism spectrum disorders (ASD) and attention deficit hyperactivity disorders (ADHD) being a common feature of the syndrome (Schnieder et al., 2014). 22q11DS is also one of the strongest known risk factors for schizophrenia spectrum disorders (SSD), and a significant body of literature has addressed SSD risk in the 22q11DS population (Owen, 2016).

While there is a significant body of research focused on the prevalence of and risk factors for psychiatric conditions in adults with 22q11DS, research examining factors that may influence social and educational outcomes during development is of obvious significance to individuals, families, and clinicians (Swillen, 2016). Cross-sectional investigations suggest that both social and educational outcomes are impacted for individuals with 22q11DS, but the relationship between neurodevelopmental difficulties and outcomes is not well understood (Curtin et al., 2021). This systematic review will therefore examine the longitudinal literature relating to neurodevelopmental trajectories in 22q11DS, with a view to elucidating the impact of these trajectories on the social and educational functioning of CYP living with the syndrome.

A Note on Language

It should be noted that service users have emphasised the need for a move toward more neuroaffirmative language in research and practice (O'Neill & O'Donnell, 2024; Rosqvist et al., 2023). While the terms ASD and ADHD are diagnostic labels often used in the literature around 22q11DS, I recognise the movement away from discussing 'disorders' and therefore, where possible within the review, I have referred to 'conditions' or 'differences.'

22q11DS Neurodevelopmental Phenotype

Neurodevelopment comprises several domains of development and many of these have been investigated in the 22q11DS population. General cognitive development, language development and the development of executive functioning capabilities have been examined in the context of 22q11DS, alongside the presence of neurodevelopmental conditions such as ASD and ADHD (Schnieder et al., 2014). Given that disturbances in neurodevelopment are understood to be one of the most important precursors to poor social and educational

functioning in adulthood, neurodevelopmental trajectories are an important target of investigation in this population (Rutter et al., 2006).

General Cognitive Development

Most individuals with 22q11DS score in the borderline to mild intellectual disability range on standardised tests of cognitive ability, and many experience learning difficulties (De Smedt et al., 2007). A recent meta-analysis of cross-sectional studies found large and heterogeneous effects on several domains of cognition in a 22q11DS sample (Moberg et al., 2018). However, cognitive abilities may not be stable during neurodevelopment, and cross-sectional studies are not well placed to detect differences in abilities across development.

In the longitudinal literature relating to cognitive development, one study found a modest but significant decline in full scale IQ from age 8-24 in a 22q11DS sample (Vorstman et al., 2015). However, another longitudinal study did not detect a decline in cognition, with the authors concluding that changes in IQ were likely to be normal fluctuations across development, rather than representative of a syndrome specific decline (Chawner et al., 2017). There is some evidence of differential trajectories in general cognitive ability, which include a relatively stable IQ trajectory, an absolute decrease in IQ (most notable in the Verbal IQ index), and a lack of cognitive development meaning that individuals grow into deficit (Duijff et al., 2013; Swillen & McDonald-McGinn, 2015). Many of the above studies have sought to link differential cognitive trajectories in individuals with 22q11DS to SSD risk. However, links between cognitive trajectories and social and educational outcomes are also an important area of investigation for CYP with 22q11DS and their families, given the importance of social and educational functioning to quality of life (Land et al., 2012).

Language Development

Children with 22q11DS often experience speech problems due to velopharyngeal insufficiency, a malformation of the palate which impacts on the ability to make speech

sounds, and this has been central to research around communication in the syndrome (Mills et al., 2006). However, difficulties in both receptive and expressive language abilities, often exceeding the level that would be predicted by the child's cognitive ability, have also been noted in children with 22q11DS without physical difficulties (Glaser et al., 2002, Solot et al., 2001). Receptive language skills comprise an individual's ability to comprehend language, while expressive language skills involve the ability to communicate with others using language (Singleton & Shulman, 2013). Selten et al. (2021) found that receptive language skills were significantly lower in children with 22q11DS than in age matched children with developmental language delay.

In typically developing populations, receptive skills tend to predate and drive expressive skills (Singleton & Shulman, 2013). However, a separate profile of expressive skills exceeding receptive skills has been observed in ASD populations (Woynaroski et al., 2015). Given the high prevalence of ASD in the 22q11DS population, the language profile of children with 22q11DS has been investigated. Comparisons with typically developing peers indicate significant difficulties in both expressive and receptive language in CYP with 22q11DS (Verbesselt et al., 2023). Another study examined language development in CYP with 22q11DS longitudinally, with comparison groups comprising children with ASD and children with idiopathic intellectual disability (IID) (Van Den Heuvel et al. (2018b). Children with 22q11DS began with an advantage of receptive over expressive skills, but unlike children with IID this diminished over time. Subtle differences in language profile were also noted between the 22q11DS and ASD groups, indicating atypical trajectories of language development in 22q11DS. Not only do language difficulties impact on an individual's ability to achieve educational success, but children with 22q11DS may struggle to use language in a social context, with an impact on peer relationships (Van Den Heuvel et al., 2016). The

impact of developmental language trajectories on social and educational functioning is therefore an important area of investigation for CYP with 22q11DS.

Executive Functioning Development

Executive functions refer to a range of cognitive processes that govern an individual's ability to flexibly adjust their thinking, perception, and behaviour (Anderson, 2002). Such skills are considered vital to higher level functioning. In the non-22q11DS literature, childhood executive functioning has been suggested to be predictive of both social outcomes (Rinsky & Hinshaw, 2011) and academic achievement (Sjöwall et al., 2015). While various models of executive functioning have been proposed (Barkley, 1998; Lezak, 1995; Miyake et al., 2000), the term generally covers the higher-level functions required to effect goal-oriented behaviour, including updating, shifting and inhibition (Miyake & Friedman 2012).

Difficulties in executive functioning abilities are commonly reported in the 22q11DS literature (Antshel et al., 2008). Much of the 22q11DS literature has focused on specific executive functioning domains (McCabe et al., 2014). Shapiro et al. (2014) noted impairments to reactive inhibition (stopping) in children with 22q11DS but found that performance on a proactive inhibition (anticipatory stopping) task was similar to controls. Meanwhile, Antshel et al., (2007) reported problems with cognitive flexibility in children with 22q11DS, when compared with controls. Similarly, investigations into spatial working memory have revealed difficulties in the 22q11DS group (Azuma et al., 2009). These findings were confirmed in a cross-sectional study examining several domains of executive functioning in CYP between seven and fourteen years of age (Shapiro et al., 2014). This study indicated difficulties with inhibition, shifting and verbal and non-verbal working memory. Executive functioning has been investigated longitudinally in 22q11DS to examine whether these difficulties resolve with age, and researchers have suggested that although

there is an improvement over time in this population, executive functioning capabilities never reach the level of typically developing peers (Chawner et al. (2017).

There is some disagreement in the existing literature around the potential links between executive functioning trajectories and social outcomes. Kiley-Brabeck & Sobin (2006) found a cross-sectional association between executive functioning and social functioning in children with 22q11DS. However, this was not replicated in a study by Campbell et al. (2015), where general cognition, but not executive function, was found to be associated with social competence. In this review, I examined the longitudinal literature in relation to aspects of executive functioning and social and educational outcomes with a view to examining these discrepancies.

Attention Deficit Hyperactivity Disorders

ADHD is a neurodevelopmental condition and is often defined by executive dysfunction, alongside symptoms of inattention and hyperactivity in childhood (Wilcutt et al., 2005). In the 22q11DS population, 15-37% of individuals meet the diagnostic criteria for ADHD (Schneider et al., 2014). The trajectory of children with 22q11DS has been noted to move from an externalising profile, with prominent behavioural difficulties in early childhood, toward an internalising profile, marked by withdrawal and social difficulties in adolescence (Philip & Bassett 2011). This change in profile is not associated with the trajectory of general cognitive ability (Duijff et al., 2013). However, the presence or absence of ADHD as a categorical diagnosis is an important area of study in 22q11DS given the link between ADHD and executive functioning, as well as links between ADHD and social and educational functioning.

Autism Spectrum Disorders

ASD is a group of neurodevelopmental conditions defined by social communication difficulties and restrictive and repetitive behaviours. It is known to impact on social

outcomes, with limited social inclusion in childhood often continuing into adulthood (Howlin et al., 2013). ASD occurs in approximately 13-27% of individuals with 22q11DS (Schneider et al., 2014). There has been some recent controversy over diagnosis of ASD in the 22q11DS population, with some suggesting that CYP with 22q11DS do not meet the full diagnostic criteria for ASD (Ogilvie et al., 2000). However, studies triangulating information using the Autism Diagnostic Interview-Revised (Lord et al., 1994), the Autism Diagnostic Observation Schedule, second edition (Lord et al., 2012), and a clinical interview, have continued to report high rates of ASD in 22q11DS samples (Ousley et al., 2017). One explanation for the controversy may be diagnostic overshadowing, with ASD symptoms being incorrectly attributed to childhood ADHD or anxiety. What is indicated in the literature is that individuals with 22q11DS and ASD experience more severe socialisation problems than individuals with ASD alone (McCabe et al., 2013). Findings also suggest that these problems are present in primary school for individuals with 22q11DS (Campbell et al., 2011) and intensify with age (Serur et al., 2019). Studies examining the longitudinal impact of ASD on social outcomes in CYP with 22q11DS are therefore an important area of investigation.

Summary of Neurodevelopmental Phenotype

The 22q11DS neurodevelopmental phenotype, while highly variable, is often marked by cognitive difficulties, difficulties with language development and executive functioning difficulties. Additionally, the syndrome carries a high risk of neurodevelopmental conditions including ASD and ADHD. The trajectories of neurodevelopment described above may influence the primary concerns of individuals and caregivers across the lifespan. Early in development, delayed achievement of language and developmental milestones may emerge, with learning difficulties and challenges linked to social communication influencing early schooling experiences and challenges linked to ADHD and social relationships emerging in adolescence (Swillen & McDonald-McGinn, 2015).

Theoretical Considerations

An important theoretical point to note is that many of the domains of functioning examined in neuropsychological research are constructs that describe higher-level functions drawing on multiple underlying skills. Neuroconstructivist theory suggests that delays in the development of individual abilities can result in a developmental cascade, impacting on the development of higher-level functions which often require individuals to draw on multiple individual abilities (D'Souza & Karmiloff-Smith, 2016). Additionally, tests of individually conceptualised abilities in a laboratory may be less valid than self-report measures of abilities in real-world settings (Barkley & Fischer, 2011). Longitudinal observations in neuropsychological development enable stronger associations to be made between core abilities and higher-level functioning, as they allow for the testing of capabilities in individuals over time.

Social Outcomes for Children and Young People 22q11DS

Social functioning can be operationalised in a variety of ways (Cook & Oliver, 2011). Domains of social functioning can include relationships with peers, family, and partners, as well as activities of daily living, leisure, and employment. More specifically, social functioning can be defined as the ability to initiate and maintain social bonds with others (Campbell et al., 2015), while social skills relate to the development of behaviours to facilitate social problem solving (Gillis & Butler, 2007). Adequate social functioning is integral to independent living, the maintenance of employment and positive interpersonal relationships (McFall, 1982), while low acceptance among peers in childhood is associated with a variety of negative outcomes (Wentzel et al., 2021).

Difficulties with social adjustment have been reported in the 22q11DS adult population (Fung et al., 2015), and in adolescents with 22q11DS (Tang et al., 2015). Children with 22q11DS have been described as having poor social skills, particularly in initiating

social relationships with peers, when compared with age matched controls with speech and language difficulties (Schonherz et al., 2014; Swillen et al., 2001).

Both ASD and ADHD are known to independently impact on social skills in typically developing children (Humphreys et al., 2016), and the high prevalence rates of these conditions in CYP with 22q11DS may partially account for social difficulties associated with the syndrome (Aduen et al., 2018; Wilkins et al., 2008). However, research indicates that individuals with 22q11DS experience an exacerbation of social skills difficulties during adolescence (Campbell et al., 2011), that this is independent of ASD diagnosis (Kates et al., 2007) and that adults with 22q11DS experience difficulties with social communication (Fung et al., 2015). One study indicated that difficulties with emotional processing skills and theory of mind represent a developmental phenotype in CYP with 22q11DS that may explain these social skills difficulties (Norkett et al., 2017). However, Vangkilde et al. (2016) examined emotion processing and theory of mind in CYP with 22q11DS and found no significant association with social functioning, competence, or skills.

Cross-sectional studies of 22q11DS populations suggest that general cognitive ability is associated with social functioning in adolescence (Campbell et al., 2015). However, the question as to whether poor social functioning is linked to the syndrome itself or rather to the cognitive profile of individuals with 22q11DS has not been adequately answered. Parent reports of social difficulties suggest a divergent profile from individuals with IID, with social communication difficulties in 22q11DS presenting as wider and more pronounced than in individuals with IID (Van Den Heuvel., 2016). It has been suggested that social difficulties may increase for adolescents with 22q11DS due to increased social demands (Swillen & McDonald-McGinn, 2015). Longitudinal observations of neurodevelopmental processes and their impact on social outcomes are therefore important for understanding how best to support CYP with 22q11DS to improve social functioning.

Educational Outcomes for Children and Young People with 22q11DS

Academic attainment is an area of notable difficulty in 22q11DS. Dependent on a child's cognitive capacities, they may experience either specialist schooling or mainstream education with additional learning support. While reading comprehension and mathematical skills are often affected (De Smedt, 2009), word decoding and rote verbal memory skills are an area of relative strength (Antshel et al., 2008). Most adolescents with 22q11DS (91%) experience learning difficulties at school (Cohen et al., 2017), and several studies have reported a steeper decline in verbal abilities than non-verbal during adolescence (Duijff et al., 2012; Duijff et al., 2013), with one paper indicating a divergent trajectory of decline in verbal skills for individuals who went on to develop SSD (Vorstman et al., 2015).

Given that several studies have reported lower levels of employment and fewer hours worked in adulthood for individuals with 22q11DS when compared with individuals with IID, educational functioning is an important aspect of development for investigation in this population (Butcher et al., 2012; Mosheva et al., 2018). It is also important to note that academic achievement is positively correlated with peer acceptance in typically developing populations, and that outcomes relating to social and educational functioning may therefore be linked (Wentzel et al., 2021). Additionally, one study examining management of 22q11DS in the classroom indicated that lack of understanding of the syndrome in education systems may exacerbate distress (Morishima et al., 2021).

Rationale for the Current Review

The risk of developing SSD by young adulthood for CYP with 22q11DS has been estimated at 41% (Schneider et al., 2014). For this reason, the syndrome has become a neurogenic model of SSD risk. Recent reviews in the 22q11DS literature have focused on risk factors for the development of SSD, specifically on neurobiological correlates (Zinkstok et al., 2019), social cognitive difficulties (Milic et al., 2021) or general cognitive development

(Fiksinski et al., 2021). One review included data on social and educational outcomes (Jhawar et al., 2021) but retained a primary focus on SSD risk. While these investigations are valid and useful, one reason to widen the focus from studies investigating SSD risk was that the findings of a large, cross-sectional study suggested that cognitive skills and adaptive functioning, and not the presence or absence of SSDs, are key factors in education and employment outcomes (Mosheva et al., 2018). The importance of educational and employment outcomes to overall quality of life means that factors influencing these outcomes are an important target for investigation (Land et al., 2012).

A further limitation of this specific focus on risk factors for the development of SSD may be that neurodevelopmental factors influencing the social and educational outcomes of CYP with 22q11DS who do not go on to develop SSD – a significant percentage of the 22q11DS population – have been overlooked (Fiksinski et al., 2021).

Exploring neurodevelopmental trajectories in relation to social and academic outcomes is important to inform the expectations of individuals with 22q11DS and enhance carers and clinicians' understanding of the needs of this population, in supporting individuals to maximise their social and adaptive functioning.

Aims

The aim of this systematic review is to describe the current knowledge base relating to the neurodevelopmental trajectories of CYP with 22q11DS, with a view to elucidating which variables best predict social and educational outcomes. To achieve this, I systematically selected longitudinal studies, where participants had 22q11DS, where neurodevelopmental trajectories were assessed, and where social or educational outcomes were reported. I then looked to answer the following questions:

- Do neurodevelopmental trajectories predict social outcomes CYP with 22q11DS when compared with control groups?

- Do neurodevelopmental trajectories in 22q11DS predict educational outcomes in CYP with 22q11DS when compared with control groups?

A narrative synthesis and interpretation of the reported data followed, highlighting critical aspects of the current state of research on the topic.

Method

Data Collection

Studies were collated and organised in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2010) and reporting followed the PRISMA-S checklist for reporting literature searches in systematic reviews (Rethlefsen et al., 2021). One reviewer conducted a search of three online databases – Medline, PsychInfo and Embase – simultaneously in Ovid, using specific search terms, in October 2023. A multiple database search increases the potential for identifying relevant studies, and these specific databases were chosen to provide a wide selection of potentially relevant psychological research. Following the removal of duplicates, a title and abstract screen was carried out to exclude articles that did not meet the inclusion criteria. A second reviewer screened five percent of retrieved studies to ensure that eligibility criteria had been consistently applied.

A full text review was then conducted for each of the remaining texts, to assess whether each met the list of inclusion criteria. Finally, forward, and backward citation searching was conducted on the included studies to identify additional relevant sources, which again were assessed for inclusion in the study. The number of excluded texts are reported in Figure 1, which provides a flow diagram of the search process.

Search Strategy

The search terms for 22q11DS were developed from the literature. A combination of Medical Subject Headings (MeSH) and free text search terms were entered to ensure the

inclusion of all relevant literature. These search terms were combined with AND to elicit papers referring to neurodevelopmental processes, conditions, or trajectories, as well as those investigating social and educational outcomes. The full search terms are provided in Table 1. The initial search identified 1,953 results and 541 duplicate references were removed prior to screening.

Table 1

Search Terms

Search terms
(exp 22q11DS Deletion Syndrome/ OR exp DiGeorge Syndrome/ or 22q11DS$ OR VCFS OR VeloCardioFacial Syndrome OR Catch-22 OR DiGeorge Syndrome)
AND
(Exp Neurodevelopmental Disorders/ OR Exp Attention Deficit Disorder with Hyperactivity/ OR Exp Autistic Disorder/ OR Neurodevelopmen$ OR ASD OR Autis$ OR ADHD OR Attenti$ OR Inattenti$ OR Developmen$ OR Trajector$ OR Longitudinal)
AND
(Outcome$ OR Social OR Educatio$ OR Attainment)

Inclusion and Exclusion Criteria

Appropriate eligibility criteria are critical to developing the research question and a PICOS framework, which considers the Population, Intervention/Exposure, Comparison group, Outcome and Study design was used in the development of these criteria (Eriksen & Frandsen, 2019). The PICOS for this study is outlined in Table 2.

Table 2

PICO-S Criteria for the Review

Criterion	Included studies
Population	Studies containing participants with 22q11DS
Intervention/exposure	Neurodevelopment (studies examining cognitive, language or executive functioning profiles and the presence of ASD and ADHD)
Comparison	Studies with a comparison group comprising one of the following were included: • Typically developing controls • Sibling controls • Controls with idiopathic intellectual disability • Participants with 22q11DS but without an additional diagnosis of ASD or ADHD
Outcome	Studies with at least one measure of social or educational functioning at follow-up were included
Study design	Studies using a within-subjects design to examine outcomes longitudinally were included in the review

The following inclusion criteria, based on the above PICO-S criteria, were applied to studies identified in the original search.

Longitudinal, Empirical, Peer-Reviewed Studies. To ensure that the highest quality evidence was accessed in the search, only empirical, peer-reviewed papers were considered for inclusion. Review articles, conference papers, poster presentations and unpublished studies were therefore excluded. Because the research question relates specifically to neurodevelopmental trajectories, cross-sectional study designs were also excluded.

Participants Diagnosed with 22q11DS. Because the population of interest was individuals experiencing 22q11DS, studies were excluded if they did not take measures from individuals with this diagnosis.

Base Measures in Childhood. Our interest in the developmental trajectories of individuals in studies with a within-subjects design required participants were under eighteen at baseline, to capture development.

Studies Examining Neurodevelopmental Trajectories. The literature relating to 22q11DS is wide and varied, relating not only to neurodevelopmental aspects of the condition but also to physical aspects such as cardiac defects. Therefore, studies were included where they contained measures relating to neurodevelopment.

Studies Measuring Social or Educational Outcomes. This review focused specifically on longitudinal study designs measuring either social or educational outcomes in CYP with 22q11DS, and therefore a key inclusion criterion was measures relating to one of these outcomes.

Studies Published in English Language. The practicalities of the review process meant that only studies with an English language version were included for full text review.

Study Selection

Following title and abstract screening, 91 studies were identified for full text review. In total, 7 were selected for inclusion into the review. At this point, forward and backward citation tracking was used to identify a further 2 relevant papers for inclusion. Figure 1 lists the studies that were included for final review (N = 9).

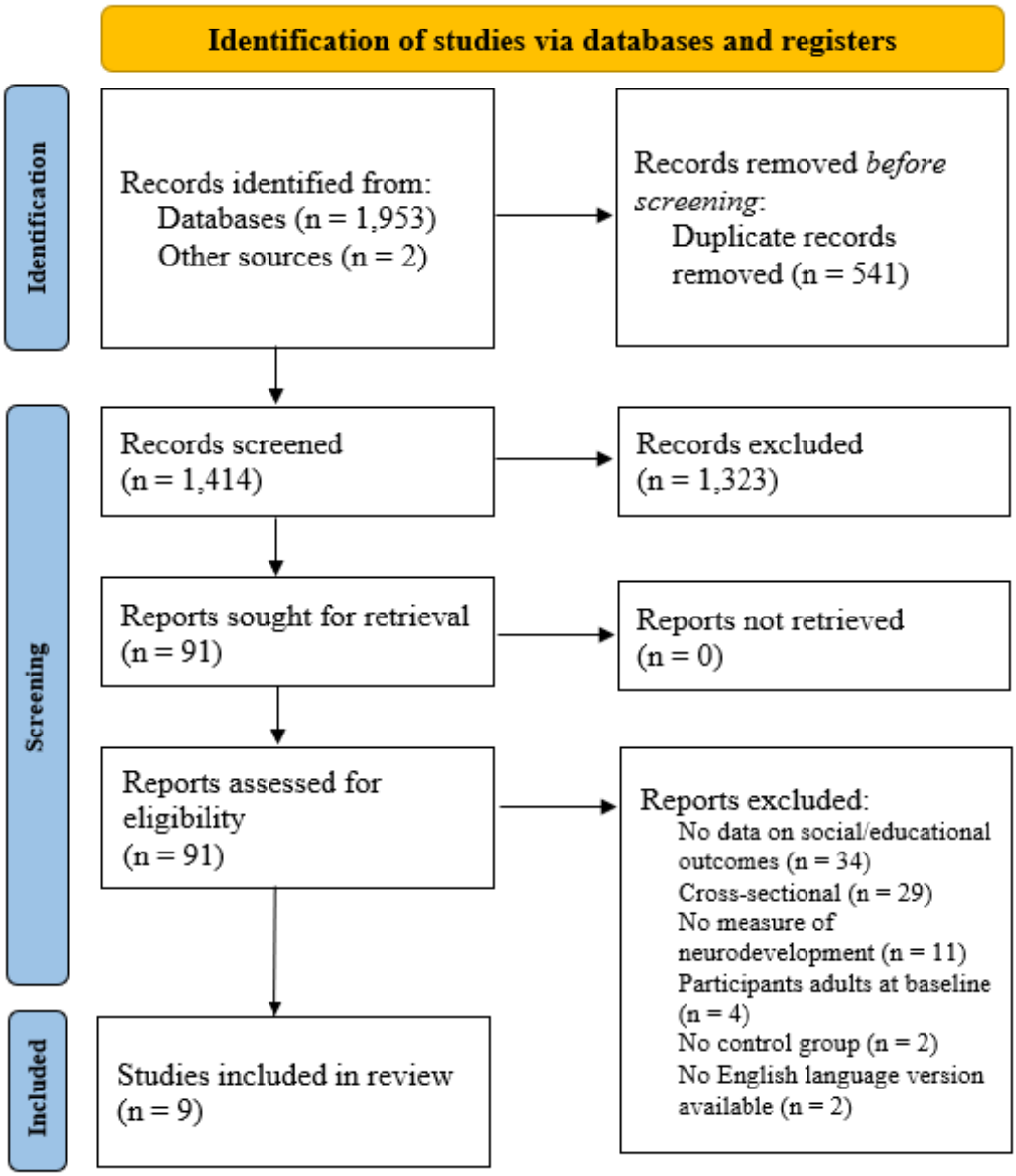
Data extraction and Analysis

Each paper was examined, and information was extracted regarding the study sample, characteristics, mean age at baseline, length of follow up and measures undertaken. Measures extracted included measures of cognition, language, and executive functioning, as well as

data relating to neurodevelopmental conditions, and measures relating to social and educational outcomes. Key findings from each study were also extracted, and the quality of papers was assessed. Notes were taken during the data extraction phase and information from the papers was then synthesised in a narrative analysis. A summary of the papers can be found in Table 3.

Figure 1

PRISMA Flow Diagram



Assessing Quality

Studies were reviewed and scored in accordance with the Quality of Reporting Observational Longitudinal Research Checklist (Tooth et al., 2005). This tool was considered appropriate due to the longitudinal, observational nature of the research being reviewed. The 33-item checklist provided a structured method of assessing the quality of observational, longitudinal studies. The checklist included sections relating to recruitment, data collection, specific biases, methods of analysis and factors such as rationale for the study, population, and generalisability. It provided a tool with which to assess the threats to external and internal validity of observational longitudinal studies.

Table 3

Studies Included in the Review

Authors, year	Title	Participants mean age (SD)	Study length	Sample	Key measures	Key findings relating to developmental trajectories and social & educational outcomes
Albert et al., 2018	Childhood executive functioning predicts young adult outcomes in 22q11 deletion syndrome	12.2 (2.3) T1 21.2 (2.2) T4	9 years	63 participants with 22q11DS 21 Sibling controls 22 Community controls	*General Cognition:* WISC-III WAIS-IV *Executive Functioning:* GDS, BRIEF, WCST, Stroop, ToL, CVLT *Social Outcomes:* VABS-II SAS Emotional intelligence questionnaire	• Slight decline in parent reported executive functioning (EF) problems from time 1 to time 4 in both 22q11DS and control group • Participants with 22q11DS demonstrated significantly greater EF impairments compared with controls, and these differences were maintained over time • EF predicted adaptive behaviour and social adjustment similarly for both individuals with and without 22q11DS • EF was uniquely predictive of emotional intelligence, externalising behaviours, and ADHD related difficulties in the study group and not the control group • No childhood variables significantly predicted employment/independent living. However, in early adulthood, controls were more likely to be employed, work more hours, and live independently than individuals with 22q11DS

Antshel et al., 2014	Predicting reading comprehension academic achievement in late adolescents with velo-cardio-facial (22q11DS deletion) syndrome (VCFS): A longitudinal study	11.9 (2.2) T1 18.2 (2.0) T3	6 years	69 participants with 22q11DS 23 sibling controls 30 community controls	*General Cognition:* WISC-III *Executive Functioning:* GDS, WCST, Stroop, VSPAN *Diagnostic:* ADI-R, BASC *Educational Outcomes:* WIAT-II	• Relative to controls, individuals with 22q11DS showed a decline in reading comprehension over time, despite a slight increase in word reading abilities • Childhood executive function (specifically working memory) predicted reading comprehension performance in the 22q11DS group only (not control group) • Neither childhood ASD nor ADHD as categorical diagnoses were predictive of reading comprehension performance in the 22q11DS group
Antshel et al., 2016	Predicting cognition and psychosis in young adults with 22q11.2 deletion syndrome	11.9 (2.1) T1 21.2 (2.2) T4	9 years	61 participants with 22q11DS 21 sibling controls 21 community controls	*General Cognition:* WISC-III or WAIS-IV *Executive Functioning:* GDS (attention) WCST CVLT, VSPAN *Educational Outcomes:* WIAT-II	• Participants with 22q11DS demonstrated differential trajectories relating to visual & auditory working memory and in academic achievement when compared with controls • While trajectories in the control group remained relatively stable, individuals with 22q11DS who went on to develop prodromal SSD symptoms performed poorly on tests of emotion recognition, word reading and cognitive flexibility
Hamsho et al., 2017	Childhood predictors of written expression in late adolescents with 22q11.2 deletion syndrome: A longitudinal study	12.2 (2.3) T1 18.0 (2.2) T3	6 years	60 participants with 22q11DS 18 sibling controls 17 community controls	*General Cognition:* WISC-III or WAIS-IV *Executive Functioning:* CPT, WCST, ToL, CVLT, VSPAN *Language:* CELF-4 *Educational Outcomes:* WIAT-II	• Children and young people with 22q11DS showed mean written expression scores 2SDs below the mean, and this result remained consistent between T1 and T3 • While childhood Verbal IQ and gender predicted written expression in both groups, executive function, and language abilities additionally and predicted written expression in the 22q11DS group only (not control group)

Hooper et al., 2013	A longitudinal examination of the psychoeducational, neurocognitive, and psychiatric functioning in children with 22q11DS deletion syndrome	10.1 (2.5) T1 13.6 (2.5) T2	3.5 years	42 participants with 22q11DS 29 controls	*General Cognition:* WISC-III *Executive Functioning:* CPT (attention), WCST, CVLT *Educational Outcomes:* WIAT-II/III *Social Outcomes:* CBCL	• Children with 22q11DS showed significantly more social behavioural difficulties than controls at both time points • Academic achievement and cognitive measures remained relatively stable between T1 and T2
Maeder et al., 2016	Developmental trajectories of executive functions in 22q11.2 deletion syndrome	12.8 (4.2) T1 Mean interval 3.68 years	Retrospective	59 participants with 22q11DS 49 controls	*General Cognition:* WISC-III WAIS-III *Executive Functioning:* CPT (attention), Stroop, Digit span (Backward), PPVT *Social Outcomes:* VABS-II	• Individuals with 22q11DS performed more poorly than controls on all EF domains • In the 22q11DS group, atypical trajectories were evident in working memory and verbal fluency, but not inhibition • Participants with 22q11DS reached a developmental plateau earlier than controls on measures of working memory and verbal fluency • These divergent trajectories remained even when controlling for IQ
Taylor et al., 2018	Young adult outcomes for children with 22q11 deletion syndrome and comorbid ADHD	12.2 (2.3) T1 21.3 (2.2) T4	9 years	29 participants with 22q11DS 23 participants with 22q11DS and ADHD	*Diagnostic:* BASC *Executive Functioning:* BRIEF, GEC, ASR *Social Outcomes*: VABS-II, SAS-SR, PAS, GAF	• Individuals with 22q11DS and ADHD at baseline experienced poorer daily social functioning at T4 than individuals with 22q11DS only • Divergence between the two groups widened over time, after controlling for EF abilities at baseline
Van Den Heuvel et al., 2018a	Exploratory study on cognitive abilities and social responsiveness in children with 22q11.2 deletion syndrome (22q11DS) and children	9.1 (2.1) T1 11.1 (2.2) T2	2 years	21 participants with 22q11DS 21 controls with IID	*General Cognition:* WISC, PPVT, CELF-4 *Social Outcomes:* SRS	• In general, the cognitive profile and trajectory of individuals with 22q11DS was similar to that of individuals with IID. • Short term memory remained a relative strength in the 22q11DS group

	with idiopathic intellectual disability					• No evidence was found that the trajectory for verbal intelligence was associated with cognitive decline in a significant subgroup of individuals with 22q11DS
Wagner et al., 2017	Childhood predictors of young adult social functioning in 22q11.2 deletion syndrome	11.9 (2.3) T1 21.3 (2.2) T4	9 years	53 participants with 22q11DS 18 sibling controls 16 community controls	*General Cognition:* WISC-III *Executive Functioning:* CPT, ToL, WCST, Stroop *Social Outcomes:* SAS, VABS	• Longitudinally investigated childhood factors as contributors to poor social functioning • General intelligence and EF in childhood did not predict social functioning outcomes for those with 22q11DS relative to controls • A relationship between internalising symptoms in childhood and social function in adolescence was established, and this was moderated by parental stress

Note: ADI-R = Autism diagnostic interview (Lord et al., 2012); ASR = Adult self-report scale (Hines et al., 2012); BASC = Behaviour assessment system for children (Kamphaus & Reynolds, 2015); BRIEF = Behaviour rating inventory of executive function (Gioia et al., 2000); CBCL = Child behaviour checklist (Achenbach & Rescorla, 2001); CELF = Clinical evaluation of language fundamentals, fifth ed. (Wiig et al., 2013); CPT = Continuous performance task, Gordon diagnostic system (Gordon et al., 1996); CVLT = California verbal learning test (Delis et al., 1988); GAF = Global assessment of functioning (Hall, 1995); GEC = Global executive composite (Gioia et al., 2000); PPVT =Peabody picture vocabulary test (Dunn & Dunn, 1997); SAS-SR = Social adjustment scale-self report (Gameroff et al., 2011); SRS = Social responsiveness scale (Constantino & Gruber, 2012); ToL = Tower of London (Shallice, 1982); VABS-II = Vineland adaptive behaviour scales, second ed (Sparrow et al., 2016); WAIS-IV Wechsler adult intelligence scale, fourth edition (Wechsler, 2008); WCST = Wisconsin card sorting task (Grant & Berg, 1948); WIAT-II = Wechsler individual achievement test (Wechsler, 2001); WISC-III = Wechsler intelligence scale for children, third ed (Wechsler, 1991)

Results

Study Characteristics

Table 3 presents a summary of the nine papers that were included in this review. Of note, six of the papers were drawn from the same sample of individuals, who were engaged in a longitudinal follow-up of adolescents with 22q11DS via SUNY Upstate Medical University, New York (Albert et al., 2018; Antshel et al., 2014; Antshel et al., 2016; Hamsho et al., 2017; Taylor et al., 2018; Wagner et al., 2017). One paper related to a longitudinal cohort recruited at Duke University Medical School and Wake Forest Baptist Medical Centre, North Carolina (Hooper et al., 2012). The remaining two studies recruited participants from medical centres in Geneva (Maeder et al., 2016) and Belgium (Van Den Heuvel et al., 2018a).

The measures of neurodevelopment used in each study are noted in Table 3. Domains of neurodevelopment investigated varied between studies, but included measures of general cognition, executive functioning, language skills and the presence of ASD and ADHD. Six of the studies within this review investigated the impact of neurodevelopmental trajectories on social outcomes, while four examined the impact of neurodevelopmental trajectories on educational outcomes. Only one paper reported measures of both social and educational outcomes (Hooper et al. 2013).

The six studies examining social outcomes as a dependent variable assessed individuals over time points between two and nine years. Three of these papers drew participants from a sample enrolled in the longitudinal study of 22q11DS at SUNY Upstate Medical University (Albert et al., 2018; Taylor et al., 2018; Wagner et al., 2017). One study used a retrospective design using pre-existing data (Maeder et al., 2016). Most studies measured social functioning using the Vineland Adaptive Behaviour Scales, second ed. (Sparrow et al., 2016). Alternative measures included the Social Responsiveness Scale

(Constantino & Gruber, 2012) and the Child Behaviour Checklist (Achenbach & Rescorla, 2001).

The four studies examining educational outcomes as the dependent variable assessed participants over time points between 3.5 and nine years. Three of these papers drew participants from a sample enrolled in the longitudinal study of 22q11DS at SUNY Upstate Medical University (Antshel et al., 2014; Antshel et al., 2016; Hamsho et al., 2017). The fourth study sampled a cohort of individuals with 22q11DS in North Carolina (Hooper et al., 2013). All four studies assessed educational outcomes using the Wechsler individual achievement test, second ed. (Wechsler, 2001).

Study length varied between two years (Van Den Heuvel et al., 2018a) and nine years. Maeder et al.'s (2016) paper was the only investigation that included a retrospective design. All other studies used a prospective, longitudinal design. While some papers investigated SSD symptoms and links between cognitive development and SSD outcomes, this review focused on the findings relating to neurocognitive development and social and educational outcomes.

Quality of studies

The 33-item checklist from the Quality of Reporting Observational Longitudinal Research Checklist (Tooth et al., 2005) was applied to each of the nine studies to assess overall quality. The checklist was used to assess quality across several domains, including issues relating to recruitment, data collection, biases, methods of analysis and other factors including rationale, population, and generalisability. Each paper was assessed, and scores were converted to a percentage. The adherence of each study to the quality criteria is noted in table 4, and detailed quality scores can be found in Appendix A. A score of over 50% on this checklist has been suggested as an appropriate measure of quality by the authors. Although some papers fell slightly below this measure, the gaps in reporting were around criteria such

as describing the sample and justifying the number of participants, with some papers noting that participants were already enrolled into a longitudinal study and were simply undertaking additional measures (Hamsho et al., 2017), or describing the measures, where measures were very well known (Hooper et al., 2013). I therefore decided to include these studies in the review, despite some discrepancies in the quality of reporting.

Table 4

Quality scores

Author, year	Quality score (%)
Albert et al., 2018	58%
Antshel et al., 2014	67%
Antshel et al., 2016	64%
Hamsho et al., 2017	48%
Hooper et al., 2013	42%
Maeder et al., 2016	45%
Taylor et al., 2018	76%
Van Den Heuvel et al., 2018a	58%
Wagner et al., 2017	67%

Participants and Recruitment

All studies recruited CYP with molecularly confirmed 22q11DS. In addition, eight studies included a control group of individuals without 22q11DS. Details on sampling, matching of controls and attrition was a strength across the studies. Controls were generally made up of age and gender matched siblings, and age and gender matched community controls. Some studies combined both siblings and community participants into one control group (Albert et al., 2018; Hamsho et al., 2017). While exclusion criteria were applied, most studies did not attempt to exclude individuals with IID, ASD or ADHD due to the prevalence

of these conditions in the 22q11DS group. Two studies specifically oversampled community participants with ADHD or intellectual disabilities to match the 22q11DS group (Antshel et al., 2014; Hamsho et al., 2017). The study which did not have a sibling/community control group compared individuals with 22q11DS+ADHD to individuals with 22q11DS only (Taylor et al., 2018).

Data Collection

All studies included a detailed description of data collection. However, fewer studies commented on the reliability of measures and only three noted the validity of the measurements used (Antshel et al., 2014; Antshel et al., 2016; Wagner et al., 2017). Although most of the measures used were well established tools, comments on the rationale for their use would have enhanced the quality of the studies.

The six papers emerging from SUNY Upstate Medical University included an analysis on attrition over the course of the study, with the remaining papers excluding comments on whether those lost to follow up differed from those remaining in the study. While all studies outlined the number of participants, no papers attempted to define non-consenters or quantify those that did not meet eligibility criteria.

Risk of Bias

None of the papers under review attempted blinding of the study or control groups. However, this is understandable given that 22q11DS is often identifiable by clinicians. Hooper et al. (2013) addressed the fact that examiners were not blinded to either the intent of the study or the participant's group. Similarly, Antshel et al. (2016) stated blinding had not been possible due to the wide geographical reach of the study and the fact that sibling controls often accompanied study participants to neuropsychological testing. However, they analysed data in the absence of participant identifiers. All the studies reviewed addressed loss to follow up in relation to risk of bias and adequately accounted for this in their analysis.

While many of the papers attempted to control for confounding variables, no studies considered the impact of family influences or interventions (such as the presence or absence of Education Health and Care Plans for individual participants).

Methodological and Analytical Considerations

While many of the studies sought to measure executive function, only two papers referenced the theoretical model they were using to understand this construct (Hamsho et al., 2017; Wagner et al., 2017). Where studies did not organise testing arrangements around an accepted model of executive functioning, measures selected may have lacked the sensitivity to detect the individual constructs of updating, shifting and inhibition (Miyake & Friedman, 2012). Similarly, papers differed on using self-report, parent-reported or clinician rated measures of social functioning. The domains of social cognition are theoretical constructs, and it has been suggested that reduced performance on clinician rated measures of social skills is not predictive of real-world social competence (Morrison et al., 2020).

Impact and Generalisability

All nine of the studies related their results back to the target population and discussed generalisability in their conclusions. Six of the studies reviewed used the same sample. While this is relatively common in rare genetic disease research, due to the difficulties experienced in recruiting participants to study centres, it does have an impact on the generalisability of findings. Where studies confirmed results using repeated sampling of the same individuals, this has been highlighted in the discussion section. The heterogeneity of comparison groups between the studies is also a limitation in the generalisability of findings. Studies used a variety of sibling controls, matched community samples and samples with IID. Finally, studies used varying measures ostensibly to test the same concepts, making it difficult to compare results between studies.

Key findings

The aims of the study were to review the included studies to answer the research questions:

a) Do neurodevelopmental trajectories predict social outcomes in CYP with 22q11DS when compared with controls?
b) Do neurodevelopmental trajectories predict educational outcomes in CYP with 22q11DS when compared with controls?

Data relevant to answering the research questions was extracted from the nine studies within the review. Six of the studies investigated social outcomes in CYP with 22q11DS, while four studies investigated educational outcomes for this population.

Neurodevelopmental Predictors of Social Outcomes

General Cognitive Ability. Hooper et al. (2013), Van Den Heuvel et al. (2018a) and Wagner et al. (2017) investigated the relationship between general cognitive development and social outcomes. The 22q11DS group performed significantly lower on measures of both cognition and social functioning (Hooper et al., 2013; Wagner et al., 2017). However, full scale IQ did not predict social functioning in young adulthood, after controlling for baseline social functioning, in either the 22q11DS group or the control group. Van Den Heuvel et al. (2018a) compared a group with 22q11DS to a sample with IID to discover whether trajectories of general cognitive ability were similar between the groups. The researchers found that the predicted sub-category of individuals experiencing an absolute decline in IQ is not unique to 22q11DS, but also occurred in their IID group, although it should be noted that this study involved younger children and ran for a shorter period than most of the studies included in this review. There is little current support for general cognitive ability as a predictor of social outcomes in individuals with 22q11DS.

Executive Functioning. Three of the studies reported trajectories of executive functioning over time (Albert et al., 2018; Maeder et al., 2016; Wagner et al., 2017). Each study measured social functioning using the Vineland Adaptive Behaviour Scales (Sparrow et al., 2016, with Wagner also applying the Social Adjustment Scale-Self Report (Gameroff et al., 2011). However, a differential battery of executive functioning tests was used across the studies. All three studies noted executive functioning difficulties in children with 22q11DS across timepoints, when compared with controls. However, there was some divergence in the findings. Maeder et al., (2016) reported atypical developmental trajectories on only two domains of executive functioning in the 22q11DS group. Participants with 22q11DS appeared to reach a plateau more quickly than typically developing peers on measures of working memory and verbal fluency, but not on inhibition, where trajectories were similar between individuals with 22q11DS and controls. In this study, divergent trajectories of development in the study group were maintained even when IQ was controlled for. However, in a longer, prospective study, it was found that participants with 22q11DS began with and maintained greater difficulties in all three executive functioning domains when compared with controls (Albert et al., 2018).

Despite the findings relating to divergent trajectories of executive functioning development, none of the studies reported a significant longitudinal relationship between executive functioning and social outcomes in either the 22q11DS group or in the control groups. This was the case whether social outcomes were measured psychometrically (Wager et al., 2017), with parent reports (Albert et al., 2018; Maeder et al., 2016; Wagner et al., 2017) or in real world measures (Albert et al., 2018). Executive functioning was, however, uniquely predictive of emotional intelligence, externalising problems, and ADHD problems in the 22q11DS group, even after controlling for IQ (Albert et al., 2018).

Neurodevelopmental Conditions. Taylor et al. (2018) was the only study to examine social outcomes in individuals with 22q11DS with ADHD and compared this group to individuals with 22q11DS only. This study found that individuals diagnosed with both 22q11DS and ADHD at baseline exhibited poorer social functioning at follow-up. Furthermore, differences between the two groups widened over time, even after controlling for executive functioning abilities at baseline.

Neurodevelopmental Predictors of Educational Outcomes

General Cognitive Ability. Hooper et al. (2013) was a relatively short study of 3.5 years, examining cognitive ability and educational achievement in late childhood. The study detected divergent trajectories of development in general cognition, with the 22q11DS group showing slower gains than the control group. Although the study did not detect divergent trajectories in academic achievement between the two groups, the authors acknowledged that the study may have been underpowered to detect such differences. Antshel et al. (2014), Antshel et al. (2016) and Hamsho et al. (2017) all identified lower functioning on both cognitive and academic measures in the study group when compared with the control group. However, significant group x time interactions were not reported, indicating that general cognitive ability predicts academic performance similarly for individuals with and without 22q11DS.

Executive Functioning. Both studies examining executive functioning uncovered divergence in executive functioning trajectories between the 22q11DS group and control group. Antshel et al. (2014) found that executive functioning abilities uniquely predicted reading comprehension performance in the 22q11DS group. Similarly, Hamsho et al. (2017) found that executive functioning abilities uniquely predicted written expression in the study group.

Language Skills. Hamsho et al. (2017) was the only study to examine language skills as a predictor of academic achievement. The authors found that alongside executive functioning skills, language skills also independently predicted adolescent written expression in the 22q11DS group and not the control group.

Neurodevelopmental Conditions. Hooper et al. (2013) investigated attention and found that the 22q11DS group experienced a significant and differential slowing of growth in their attention over time, although this did not appear to impact on academic achievement. This was replicated by Antshel et al. (2014), who reported that neither categorical diagnoses or dimensional measures of childhood ASD or ADHD predicted reading comprehension abilities in late adolescence.

Discussion

Longitudinal studies investigating the neurodevelopmental trajectories of CYP with 22q11DS, with a focus on social and educational outcomes, were systematically reviewed. Nine articles were included within the review, all of which had been published within the last ten years. The first aim of this review was to investigate whether neurodevelopmental trajectories predict social outcomes in individuals with 22q11DS when compared with control groups. The second aim was to investigate whether neurodevelopmental trajectories predict educational outcomes in individuals with 22q11DS when compared with control groups.

Neurodevelopmental Predictors of Social Outcomes

Cross sectional studies of 22q11DS populations have suggested that general cognitive ability is associated with social functioning in adolescence (Butcher et al., 2012; Campbell et al., 2015). Within the longitudinal studies included in this review, although the 22q11DS group were noted to be lower functioning on measures of both cognition and social functioning than typically developing peers (Hooper et al., 2013; Wagner et al., 2017), there

was no support for a general cognition as a predictor of social outcomes in either the 22q11DS or the control group. This suggested that performance on IQ tests did not predict social outcomes for CYP with or without 22q11DS.

There was some discrepancy in the findings relating to executive functioning. Although divergent trajectories of executive functioning development were noted across the studies, Maeder et al., (2016) failed to find a divergent trajectory in the domain of inhibition. This is likely due to differences in the executive functioning test battery between studies. The studies did not find a longitudinal relationship between executive functioning and social outcomes in either the 22q11DS group or in controls, and this finding was consistent across studies (Albert et al., 2018; Maeder et al., 2016; Wagner et al., 2017). However, it should be noted that all three studies were conducted at the same centre, with potentially overlapping participants. Therefore, the results should be treated with caution until they are replicated in an independent sample. This is particularly important given that the findings indicated a divergence from the non-22q11DS population, where childhood executive functioning in typically developing children is thought to predict social outcomes (Rinsky & Hindshaw, 2011).

The finding from Taylor et al., (2018) suggested that ADHD was predictive of social outcomes and that individuals with ADHD + 22q11DS experienced poorer social outcomes than those with 22q11DS only. However, the study was not sufficiently powered for the researchers to apply a Bonferroni correction, and these results should therefore be treated with caution. Given that research with typically developing children has indicated that ADHD may predict social outcomes in young people (Humphreys et al., 2016), this finding warrants further investigation.

Neurodevelopmental Predictors of Educational Outcomes

Divergence of measures of verbal comprehension and perceptual reasoning seen in the cross-sectional literature (Solot et al, 2001; Verbesselt et al., 2023) were confirmed in the longitudinal studies, with Antshel et al. (2014) identifying a decline in reading comprehension over time in individuals with 22q11DS, despite the expected increase in word reading abilities. Although the studies under review all identified lower functioning on both cognitive and academic measures between the study group and the control group, general cognitive ability was found to predict educational outcomes similarly for CYP with and without 22q11DS.

The two studies under review examining executive functioning and educational outcomes both found that executive functioning abilities uniquely predicted educational outcomes in the 22q11DS group (Antshel et al., 2014; Hamsho et al., (2017), although again it should be noted that these studies used the same samples. Furthermore, alongside executive functioning skills, language skills were found to independently predict adolescent written expression in individuals with 22q11DS, but not controls. While executive functioning has also been found to be predictive of school achievement in the non-22q11DS literature (Sjöwall et al., 2015), the above findings indicate that this relationship was significantly stronger in the 22q11DS group than the control group.

Finally, no relationship was found between ADHD or ASD and educational outcomes in the two studies that examined neurodevelopmental conditions as predictive factors for educational outcomes in the 22q11DS population (Antshel et al., 2014; Hooper et al., 2013).

Strengths and Limitations of the Review

This review was the first, to the authors' knowledge, to focus on the impact of neurodevelopmental trajectories on social and educational outcomes, without a core focus on SSD risk. The review contains a comprehensive quality assessment of studies and outlines the current state of research in the area. Despite the deeper insights that longitudinal studies into

the experience of individuals with 22q11DS provide, there remain significant gaps in our understanding of the neurodevelopmental trajectories of individuals with the condition.

Firstly, the existing literature focuses on individual skills and neglects potential confounding variables relating to the environment. There remain gaps in the state of knowledge relating to the impact of socioeconomic factors, family factors, interventions such as speech and language therapy, or educational interventions such as Education Health and Care Plans and targeted academic support on social and educational outcomes. Environmental factors are therefore appropriate targets for further longitudinal observation.

Secondly, as is typical of rare-disease populations due to difficulties in recruitment and a small potential pool of participants, many of the studies included in this review used the same cohort of participants in their investigations. Although the reality of recruiting through large hospital centres is that participants will often be shared between studies, this has implications for the generalisability of findings.

Thirdly, most of the longitudinal studies in this area did not include ecologically valid outcomes that would provide information about individuals' real-world functioning. Including measures such as high school grades, graduation, employment, and hours worked provides important information as to real-world functioning in this group. This is particularly important given that outcomes on psychometric tests tend to be poor predictors of real-world functioning (Stanovich, 2010).

Fourthly, research with typically developing adolescents suggests that academic performance correlates positively with social acceptance (Wentzel et al., 2021). It is possible then that social and educational outcomes in 22q11DS are linked and there is little extant research examining the interaction between educational and social experiences.

Finally, there is a distinct lack of qualitative data relating to individuals, and particularly CYP, with 22q11DS. Gaps remain in our knowledge and understanding of how

neurodevelopment, traumatic experiences and other environmental factors interact to influence outcomes in this group. Theory around SSD risk in the 22q11DS population suggests that there may be a complex interplay between genetic risk and the environmental factors often present for CYP with 22q11DS (Calvete et al., 2014), such as multiple surgeries, family stress caused by managing a complex health condition and a lack of understanding of 22q11DS in education, which may impact on individual experiences. No research has examined from a qualitative perspective the impact of this on CYP, socially, educationally, and psychologically, and this requires further investigation.

Implications for Research and Practice

Given the diverse manifestations of 22q11DS, research relating to social and educational outcomes for this population are of great interest to individuals with 22q11DS, parents and clinicians alike. It is generally accepted that educational and neurodevelopmental specialists should form an integral part of a multidisciplinary approach to managing 22q11DS. Current best practice guidelines suggest timely assessment of neurodevelopmental needs, including the involvement of psychologists (educational and clinical) and psychiatrists with knowledge of 22q11DS (Habel et al., 2014). However, current guidelines stop short of advocating for proactive management of individuals with 22q11DS in educational or healthcare settings. The impact of specific interventions, in either NHS or educational settings, is rarely discussed in the literature and is an under-researched area. The evidence contained within this review supports specific executive functioning development programmes for CYP with 22q11DS, which have been found to be most effective with individuals with poorer baseline executive functioning and ADHD (Diamond et al., 2016). It also supports the active management of ADHD symptoms in children with 22q11DS, a condition that has thus far been undertreated in this group (Tang et al., 2014).

Given the findings of this review, further research is required to establish whether ADHD symptoms uniquely predict social outcomes in individuals with 22q11DS, when compared with controls. Other research directions could include the assessment of the impact of targeted interventions and support on social and educational outcomes for young people, in order to work toward evidence-based management. It is also noted that no research, to date, has qualitatively examined the experiences of CYP with 22q11DS. Such research would allow individuals with 22q11DS to express their experiences of the challenges that accompany 22q11DS and how they have managed these difficulties, with a view to providing evidence that could be used in priority setting for both research and service development.

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Section B

A Grounded Theory Exploration of the Experiences of Children and Young People with 22q11.2 Deletion Syndrome, Building a Model of Stressors and Coping Strategies

Word Count: 7,995 (313)

Abstract

Background: 22q11.2 deletion syndrome is a complex and highly variable genetic syndrome characterised by multiple complex physical abnormalities and neurodevelopmental challenges. While there are multiple studies investigating the prevalence and course of neuropsychiatric conditions in the syndrome, qualitative enquiry into the experiences of children and young people with the syndrome represents a gap in the literature. **Method:** A qualitative, modified grounded theory methodology was used. Ten children and young people (aged 10-15) with 22q11.2 deletion syndrome were invited to take part in a semi-structured interview. Interviews were transcribed and encoded, and a theoretical model was developed. **Results:** Analysis led to the development of a theoretical model with ten related categories. The categories included neurodevelopmental difficulties, the burden of diverse medical and physical challenges, navigating education, navigating peer relationships, feeling different, the power of a responsive support system, the roots of anxiety, developing a sense of self, building independence and proactive coping. A structural model illustrates the interrelationships between categories in the model. **Conclusion:** Our findings suggest that children and young people with 22q11.2 deletion syndrome experience multiple stressors linked to educational, healthcare and in peer relationship contexts and that these experiences can have a wide-reaching impact across different areas of the child's life. Furthermore, experiences in these domains can lead to children feeling different from peers. The presence of supportive relationships was found to have an impact on children's ability to build a sense of self, develop independence and engage in proactive coping strategies. The model also considers the impact of anxiety and avoidance on children's experiences.

Keywords: 22q11.2 Deletion Syndrome, Children and Young People, Neurodevelopment, Stress, Coping

Introduction

22q11.2 Deletion Syndrome

22q11.2 deletion syndrome (22q11DS) is a genetic syndrome associated with the microdeletion of DNA on the long arm of chromosome 22 (McDonald-McGinn et al., 2015). The syndrome is characterised by multiple complex physical abnormalities (Miller, 2008), alongside a neurodevelopmental phenotype comprised of increased risks of developmental delay, learning disabilities, and a range of neurodevelopmental and psychiatric conditions (Schneider et al., 2014).

The expression of the syndrome is highly variable both between individuals and across the lifespan. Individuals' experiences of 22q11DS can therefore range from the presence of multiple complex conditions to only one or two associated features (McDonald-McGinn & Sullivan, 2011). The syndrome can present different challenges for children and their families at different developmental stages (Max Appeal, 2012). Cardiac defects and feeding difficulties can predominate in infancy, with cognitive delay and neurodevelopmental difficulties including autism spectrum conditions (ASD) often presenting in childhood, and mental health concerns emerging in adolescence (Swillen and McDonald-McGinn, 2015). Though there is a significant body of quantitative research relating to the 22q11DS neurodevelopmental phenotype, there remains a lack of qualitative research providing opportunities for children and young people (CYP) with 22q11DS to speak directly about their experiences.

Vulnerability-Stress Models of Neuropsychiatric Conditions

The role of stress in the development of neuropsychiatric conditions in the general population is well established (Bowes et al., 2015; Gur et al., 2019). Vulnerability-stress models suggest that genetic vulnerabilities interact with environmental stressors, such as

socioeconomic stress, adverse childhood experiences, or discrimination, to contribute to a developmental cascade of effects (Calvete et al., 2014). Two models in this area of research are the hypothalamic-pituitary-adrenal (HPA) axis dysfunction model and the stress sensitisation model (Collip Myin Germeys & Van Os, 2008; Walker et al., 2008).

Hypothalamus-Pituitary-Adrenal Axis Dysfunction Model

Chronic stress is understood to have a physiological impact in the general population, negatively impacting on brain development and function (McEwen, 2007). Elevations in cortisol, produced by the HPA axis in response to stress, occur in individuals who have experienced adversity in childhood, indicating long-term alterations in stress reactivity (Elzinga et al., 2010). Alterations in HPA axis functioning are associated with increased vulnerability to psychiatric conditions (Adam et al., 2017) and lower adaptive functioning (Angkustsiri et al., 2012). A study examining physiological stress reactivity in children with 22q11DS found elevated levels of cortisol, indicating the presence of chronic stress (Sanders et al., 2017).

Stress Sensitisation Model

The stress sensitisation model suggests that exposure to environmental stress in early childhood can result in more intense affective reactions to stressors in adulthood, increasing risk relating to psychiatric conditions (Collip et al., 2007). This links with cognitive models of mental health conditions, which suggest early adversity shapes negative beliefs about the self and others, impacting on individuals' affective responses to stress (Ouimet et al., 2009). Ilen et al. (2023) investigated stress sensitisation in a group of adolescents with 22q11DS and found that higher levels of perceived daily stress, when compared with controls. This suggests children with 22q11DS may be more sensitised to stress in daily life than typically developing peers.

Adverse Childhood Experiences in 22q11DS

It has been suggested that individuals with 22q11.2DS may face specific adverse experiences linked to the syndrome. The quantitative literature tells us that children with 22q11DS face medical, cognitive, and socioemotional challenges from infancy to adulthood (Beaton and Simon, 2010). Cardiac complications and palatal defects may require multiple surgeries, immunological deficiencies may require management, and difficulties with feeding and speech may require ongoing interventions (Habel et al., 2014). Additionally, evidence from the learning disability research suggests that children with additional needs, including ASD, may be at increased risk of peer victimisation (Blake et al., 2012). This may be a particular risk for children with 22q11DS, who often present with communication and learning needs alongside physical disabilities (Mayo et al., 2019).

Within the 22q11DS literature, qualitative research examining childhood adversity has sampled the parents and siblings of children with 22q11DS. Findings suggests that families navigate social stigma associated with a 22q11DS diagnosis, the need to attend multiple medical appointments, and the impact of disconnection of children with 22q11DS from their social networks (Goodwyn et al., 2017; Vo et al., 2018). Families also reported receiving inadequate support with educational and social care needs (Morishima et al., 2021). However, qualitative research on the experiences of CYP with 22q11DS is scant.

The Impact of Coping Strategies

In the general population, resilience and coping modify the physiological effect of early adversity (Schiele et al., 2020). Similar modifying effects were also reported with a 22q11DS an adolescents 22q11DS sample (Armando et al., 2018), making coping strategies in CYP with 22q11DS an important target for investigation. Individuals may draw on different cognitive strategies in responding to adversity, broadly conceptualised as active coping (taking action to mitigate the effects of the problem), and passive coping (avoidance of the

problem) (Aldwyn, 2012). In the general population, active coping is associated with coping efficacy and reduced childhood anxiety (Thorne et al., 2013), whereas passive coping is associated with internalising problems (Eisenberg et al.1997). In the learning disability research, a higher incidence of passive coping strategies was identified in CYP with a learning disability versus controls (Firth et al., 2009). However, no studies to date have examined coping strategies in children with 22q11DS.

The Impact of Communication and Social Skills

Positive social relationships are also understood to act as a buffer against adverse experiences in the general population (Wang et al., 2021). However, individuals with ASD commonly experience peer relationships difficulties and report elevated rates of social stress (van der Linden et al., 2021). This is likely relevant to CYP with 22q11DS, as a significant portion either receive a diagnosis of ASD in childhood or exhibit characteristics linked to ASD (Schneider et al., 2014). In a recent study of role play interactions, adolescents with 22q11DS performed similarly to CYP with ASD, exhibiting poorer social skills and higher social anxiety than controls (Feller et al., 2024). This indicates that social skills can be a specific area of weakness for CYP with these neurodevelopmental conditions.

Intolerance of Uncertainty and Anxiety

Intolerance of uncertainty is a dimensional construct put forward to explain the underlying processes driving the maintenance of anxiety (Birrell et al., 2011). The factors of the model are desire for predictability and uncertainty paralysis, which can be understood as contributing to avoidance and passive coping. Intolerance of uncertainty has been explored in both children (Fialko et al., 2012) and adolescents with ASD (Boulter et al., 2013) and has been found to have utility in explaining the maintenance of anxiety. It is therefore plausible that such a model could contribute to understanding anxiety in CYP with 22q11DS.

Rationale for the Current Study

Children with 22q11DS have an unusually high risk of developing a schizophrenia spectrum disorder (SSD) by young adulthood (Schnieder et al., 2014), and as such the syndrome is often treated as a neurogenic risk model for SSD. As a result, there have been multiple studies investigating the prevalence of neuropsychiatric conditions and the experiences of parents and siblings. However, there is currently a lack of direct investigation into the lived experiences of CYP with 22q11.2DS. To our knowledge, only one paper explores the views of CYP with 22q11DS qualitatively (Wray et al., 2022). However, this mixed methods study used thematic analysis and surveys to understand unmet needs for children with 22q11DS who were accessing NHS support for mental health or behavioural difficulties.

It is well established that service user perspectives should be central to priority setting in research and service development (Nygaard et al., 2019). This is in line with the NHS values relating to 'respect and dignity' and 'everyone counts,' which emphasise the need for positive experiences for individuals encountering the service and applying resources effectively. There is significant value in undertaking qualitative research designed to centre the voices of CYP with 22q11DS.

Aims

This research aims to use grounded theory to build a theoretical model that explains the unique risk and resilience factors faced by CYP with 22q11DS, providing information that may be used in priority setting for future research and interventions. To do this, the following questions were considered:

a. Which aspects of life are experienced as stressful by CYP with 22q11.2DS?
b. What strategies and supports do CYP with 22q11DS access in coping with their experiences?

Method

Design

A qualitative, modified grounded theory (GT) methodology was adopted (Glaser & Strauss, 1967). This approach is appropriate where there is little existing research in relation to a specific phenomenon or group (Birks & Mills, 2015). A core component of GT is the simultaneous gathering and analysing of data in an iterative process to build a theoretical framework (Corbin & Strauss, 1990). The inductive nature of this method was considered particularly suited to the research aims, given that no previous studies had examined the experiences of children with 22q11DS qualitatively. The GT approach allowed for theoretical development of the questions based on data that emerged through the process of data collection (Tie et al., 2019). The research aligned with a critical-realist epistemological stance, which views the process of gathering and analysing data as one of co-creating meaning in ways which correspond to an objective reality but are also influenced by context, power relationships and the researcher's personal position (Hoddy, 2018). The approach taken by Corbin & Strauss (1990) is considered compatible with critical realism (Weed, 2016). The approach was modified in that the small pool of potential participants precluded a comprehensive theoretical sampling approach. Researcher reflexivity is important in GT and a reflective journal was used to support reflexivity (Meyer & Willis, 2018).

Participants

Ten participants (aged 10-15) were recruited to the study. Participants were recruited from a specialist multidisciplinary 22q11DS clinic in a tertiary paediatric hospital and via a national 22q11DS charity. Six participants were recruited through the participating NHS site and four self-referred into the study through the charity (see Figure 1). Table 1 presents the participants' demographic information.

Figure 1

Route of Participants into the Study

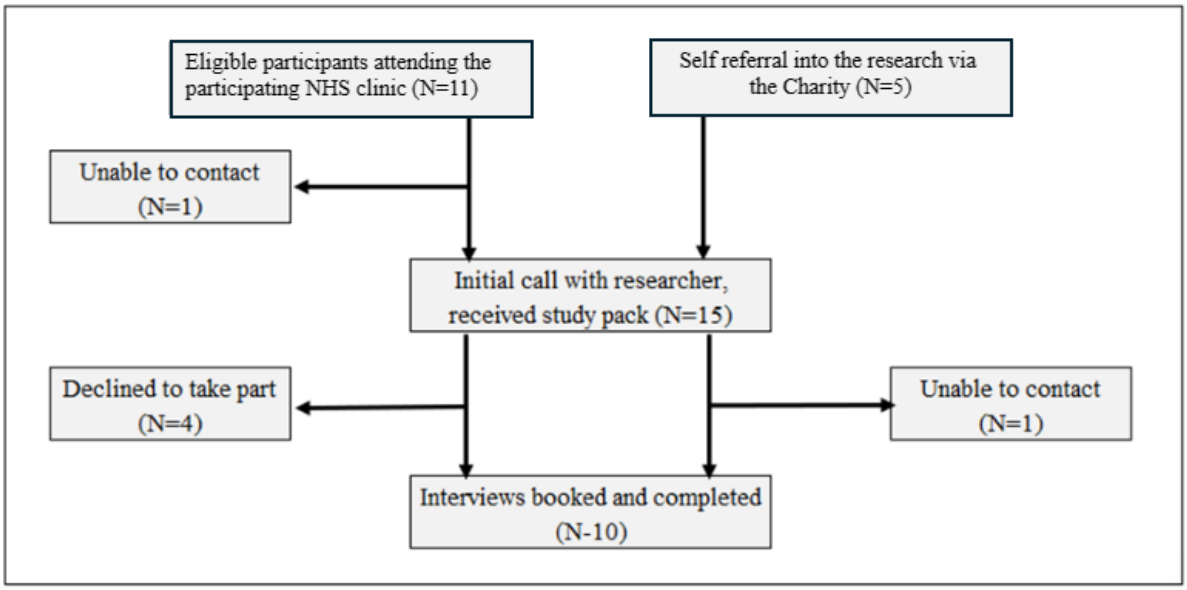


Table 1

Participant Demographics

Variable	Demographic information	Number of participants (N=10)
Gender	Female	4
	Male	6
Age	10-11	3
	12-13	2
	14-15	5
Ethnicity	White British	9
	Indian	1
School attendance	Mainstream	5
	Specialist	4
	Not currently attending	1

Measures

A semi-structured interview schedule (Appendix G) was developed by the researchers after reviewing the existing literature and theory in the field (Hoddy, 2018). Interviews were informal and used open questions and prompts (Wimpenny & Gass, 2000). A person-centred interview style was employed, and the style was adapted in accordance with best practice for interviewing children with social communication difficulties (Tyrrell & Woods, 2018).

Procedure

Recruitment and Sampling

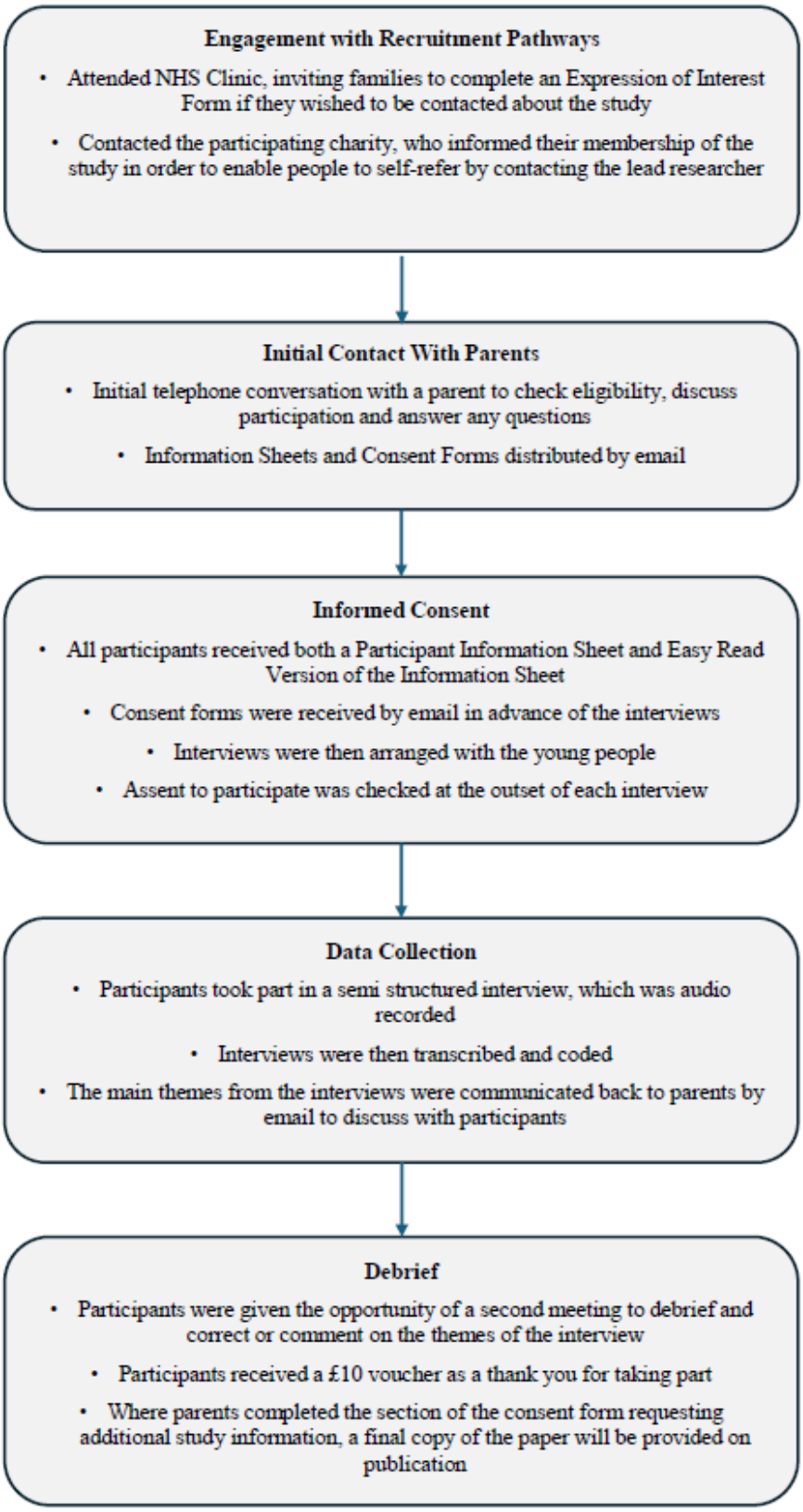
Participants were recruited through both the NHS site and self-referral route. Sampling was partly purposive, in accordance with the inclusion criteria for the study, and partly opportunistic, based on the relatively small pool of eligible participants (Payne, 2021). The sample size was arrived at after consideration of previous GT studies (Thomson, 2010) as well as practical limitations, such as the small pool of potential participants. Figure 2 demonstrates the recruitment and data collection procedures employed in the study.

Inclusion and Exclusion Criteria

Individuals were eligible to take part in the study if they were between 10-15 years old and had 22q11.2DS. This age group was chosen to capture individuals who were likely to be able to communicate about stress and coping but were within the developmental window of childhood and adolescence. Individuals were also required to have sufficient communication skills to take part in an interview with appropriate adaptations. This criterion was arrived at after considering that, given the small scope of the study, data gathered would need to be rich (Charmaz & Thornberg, 2020). Participants were excluded where their parent/guardian felt engaging in the interview may cause significant distress.

Figure 2

Recruitment and Data Collection Procedure



Participation in the Study

Parents consenting to receive study information were provided with a study pack, which included information sheets and consent forms (Appendices C-F), and the procedures shown in Figure 2 were followed. Assent to take part was checked with the young person at the outset of the interview to support participants' developing autonomy (Miller & Nelson, 2006).

Interview Procedures and Validation of Results

Interviews took place between January and April 2024 and were recorded, transcribed, and anonymised. Initial interviews followed the format outlined in Appendix G. Necessary adaptations, including rapport building, the use of visual aids, and parental support, were offered where appropriate. Following each interview, transcription and coding took place. The main themes from the interview were then communicated back to participants by email and a debrief call was offered. This enabled the child to verify or correct the interviewer's understanding where required. The interview schedule was developed iteratively, through discussion with supervisors and reflections on coding (Foley & Timonen, 2015).

Data Analysis

Data gathering, and analysis took place concurrently in an iterative process (Tie et al., 2019). After each interview, transcripts were open coded in a process where data from early interviews was 'fractured' and examined line by line for all potential meanings (Payne, 2015). Where possible, participants' own words were coded to preserve authenticity and meaning (Corbin & Strauss 2015). A second coder independently coded one of the early transcripts, to allow for verification of the emerging concepts. The development of the interview schedule constituted a form of theoretical sampling, which enabled parts of the emerging model to be tested (Sebastian, 2019). A reflective log enabled the documentation of interpretations impacting on the work (Birks & Mills, 2015).

In a process of constant comparison, codes were broken down and reorganised to create descriptive categories. Examination of the relationship between categories led to the development of a theoretical model (Corbin & Strauss, 1990). Memos and diagrams in the researchers' reflective log captured observations and facilitated elaborations around the meaning of emerging hypotheses (Corbin & Strauss, 2015). Interviews continued until conceptual depth, where categories are judged to meet the requirements of range, complexity, subtlety, and resonance, was achieved (Nelson, 2017).

Ethical Considerations

This research received ethical approval from the Health Research Authority and Health and Care Research Wales (Appendix H), as well as the participating NHS site (Appendix I). The researchers adhered to the British Psychological Society (2021) Code of Human Research Ethics, which emphasises the guiding four principles of respect, competence, responsibility, and integrity. Care was taken to avoid coercion in consent and assent procedures and to ensure confidentiality by anonymising all data. In addition, procedures for safeguarding and for managing distress were operationalised (Appendix C).

Quality Assurance Methods

Theoretical and Personal Orientation

In accordance with GT, a scoping literature search was conducted prior to forming the project proposal (Sebastian, 2019). In addition, the lead researcher kept a reflective journal, enabling the consideration of assumptions and power differentials throughout the research (Tie et al., 2019).

Prior to data collection, the researcher attended a specialist NHS 22q11DS clinic several times to enable the development of sensitivity to the issues facing CYP with 22q11.2DS. The lead researcher was a white middle-class woman with children of her own. While undertaking the research, she drew on her experiences as a parent and a clinician, who

had worked within child and learning disability services previously. At times, these experiences were helpful and facilitated greater engagement with families.

One challenge was that when recruiting from the NHS site, the researcher sat within the psychiatry clinic, as part of a multidisciplinary approach to 22q11DS. This meant that the researcher had often heard the concerns of parents prior to interviews and had therefore been experienced by the child as a clinician. The researcher noted that the participants who self-referred into the study seemed more relaxed in the interviews. In addition, it was noted that the CYP often brought different concerns to the interview than their parents had presented in a clinical context. These nuances were reflected on in supervision and a conscious effort was made on the part of the researcher to privilege the concerns that were brought by the child within the interview.

Service User Involvement

To centre service user perspectives within the research, representatives from the 22q11DS charity and an individual with 22q11.2DS were consulted at the research design stage and in the development of the semi-structured interview. The contributions of these individuals helped to shape the project in several ways, including in the development of the research question, the recruitment strategy and the content of the initial semi-structured interview. Recruiting from a wider sample than individuals attending the NHS site was suggested as a way of widening the participant pool outside of those actively seeking NHS support and including a more community-based sample of young people. The focus on experiences of education, alongside medical and social concerns, also emerged through consultation with service users.

Results

A model of the experiences of CYP with 22q11DS was developed from the data. Table 2 presents the categories, along with concepts and their properties.

Table 2

Categories, Concepts and Properties in the Model

Categories	Concepts	Examples of properties of concepts
Neurodevelopmental difficulties	Difficulties describing memories and events Difficulties communicating Developmental delay	Finding it hard to recall facts and feelings Finding it difficult to talk about surgeries Finding it hard to explain Being late to talk due to medical issues
The burden of diverse medical & physical challenges	Regular and repeated interventions Physical limitations Experiencing pain Changes after surgery	Multiple and repeated appointments Long car journeys to the hospital Difficulties standing or engaging in sports Experiencing pain around surgery Changes in function linked to surgeries Long periods of recovery
Navigating education	Academic difficulties Executive functioning difficulties The school environment A non-responsive system	Self-identified differences in learning style Getting mixed up Finding it hard to focus Experiencing learning as stressful Unpredictability of timetables Sensory issues with noise/uniforms Teachers not responding to difficulties
Navigating peer relationships	Peer relationship difficulties Barriers to forming relationships Social environmental challenges	Struggling to form peer relationships Feeling ignored Experiences of bullying Sense of powerlessness in peer relationships Awkward social contact with new people Finding others' challenging behaviour difficult
Feeling different	Sibling difficulties Experiencing 22q11.2DS Experiences of diagnosis Sensing differences from peers	Conflict with siblings Not having anything in common with others What is me? What is 22q11DS? Awareness of difference Not talking about 22q11DS Needing time alone
The power of a responsive system	Developing supportive attachments Managing physical limitations Experiences of NHS support	Finding comfort in family relationships Getting help from individual teachers Finding the right environment (school)

		Getting support around impact of physical difficulties Feeling that 22q11DS is well managed
The roots of anxiety	Difficulties separating from attachment figures The mental health burden of experiences The mental load of difficulties in peer relationships Worries about surgery Fear of the unknown	Anxiety leaving a parent Difficulties attending/returning to school (after surgery) Specific phobias Sleep difficulties Worries about school achievement Unsure of position with peers Worries about surgery Worries about the consequences of future surgeries
Developing a sense of self	Building competence Expressing creativity Engaging in leisure activities	Developing a non-academic skill (music, sports) Expressing achievement Using creative skills
Building independence	Self-soothing Building peer relationships	Time alone to focus or relax Building independence from parents Group activities with small group of friends Engaging with special interests
Proactive Coping	Preparing for changes Taking positive action	Familiar routines Getting prepared Focusing on rewards after surgery Finding enjoyment in preferred activities Staying positive about school achievement Engaging with help and support

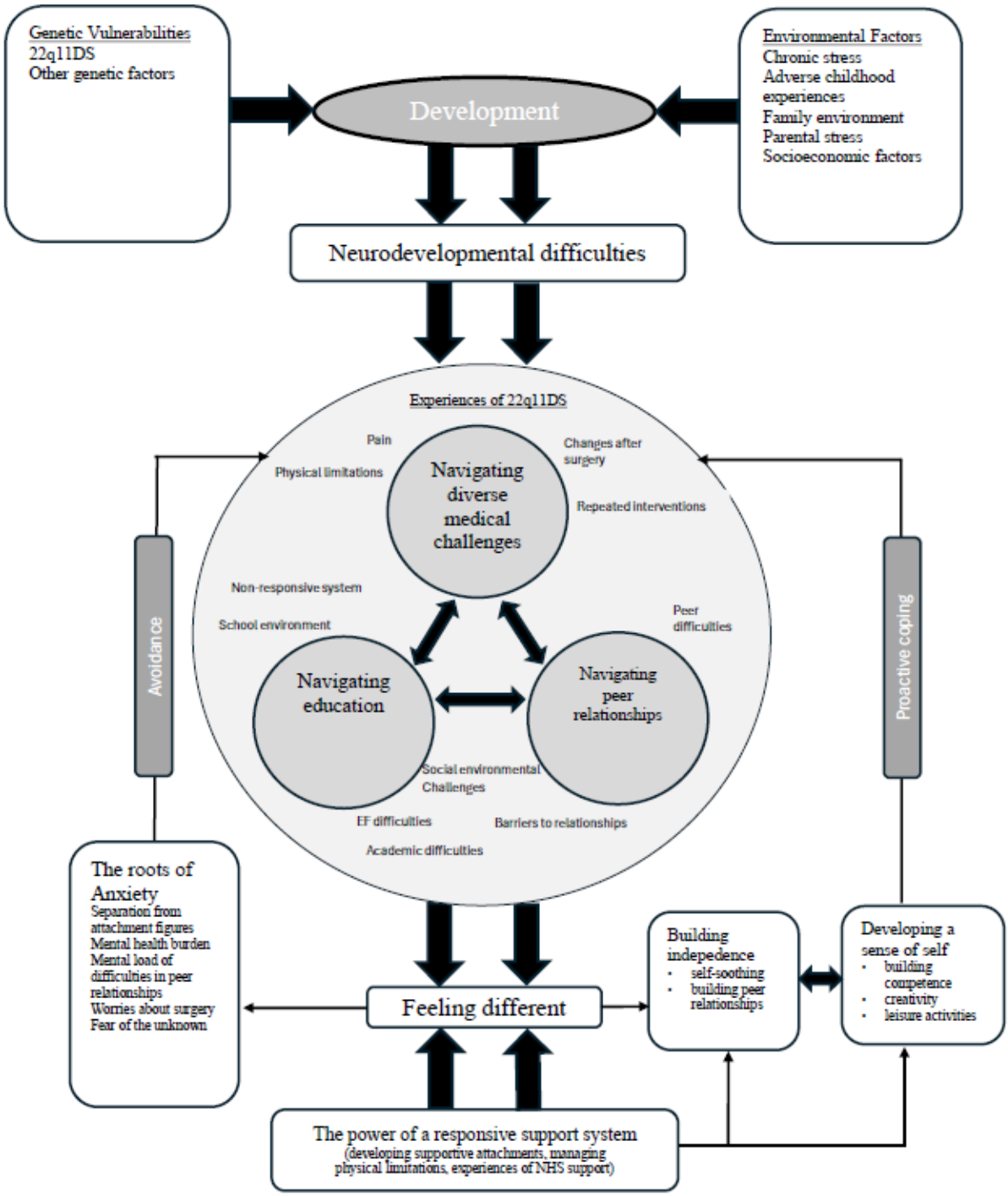
Modelling the Experiences of Children and Young People with 22q11DS

The aims of this study were to develop a theoretical model of the experiences of CYP with 22q11DS, including which aspects of life were described as stressful and the strategies and supports participants used to manage their experiences. While significant variability emerged in the experiences of participants, there were also commonly experienced phenomena which presented repeatedly within the data. These phenomena are described in the model (Figure 3).

The model begins with development, illustrating the current state of knowledge of the impact of genetic vulnerability interacting with environmental factors to influence childhood development. The model then goes on to the first category, *neurodevelopmental difficulties*. From here, the model illustrates the experiences of participants across the three categories of *the burden of diverse medical & physical challenges, navigating education,* and *navigating peer relationships*. The model demonstrates the interrelationships between these experiences, where negative experiences often reverberate across the domains. It then goes on to explain the impact of these experiences on participants *feeling different*. At this stage, the *power of a responsive support system* added to the child's resources in managing challenges. The category *the roots of anxiety* contributed to negative feedback loops of avoidance, whereas *developing a sense of self* led to participants *building independence* and developing *proactive coping* skills. Coping was linked with and influenced by the support available within the family, school environment and the child's wider system.

Figure 3

Model of Stress and Coping in Children and Young People with 22q11DS



Neurodevelopmental Difficulties

The first category captured *neurodevelopmental difficulties.* Difficulties emerged from both the content of the data and the process between the interviewer and participants. The concepts within this category included *difficulties describing memories and events*, *difficulties communicating* and *developmental delay.*

Difficulties Describing Memories and Events. Participants often struggled to recall memories of pertinent events, such as experiences of bullying and thoughts and feelings around recent surgeries. The quote below included discussions about a surgery that had happened a year previously, when the participant was fourteen:

> *Well, I had to have a surgery on my palate. I remember, like, I felt a bit like dizzy. It's hard to remember though. (P10)*

Problems with remembering were present across multiple contexts and presented a challenge for participants, with implications for daily functioning:

> *I have noticed that…I ask a question, or I say a statement or I, like, tell a joke or something. And then the day after I completely forget about that previous incident and then I do the exact same thing. (P4)*

Difficulties Communicating. Difficulties with communication were present throughout the data, often represented by silence, or in answers such as *"I'm not sure."* (*P1*) However, when the process was explored, some richer explanations emerged. This statement illustrates the impact of communication difficulties, where participants described bodily sensations linked to distress, but found it difficult to attribute thoughts to these experiences:

> *I don't know…How does it affect me? I'm not sure how it feels. But it does affect me because I'm, like, panicking. (P2)*
>
> *I don't really know how to explain it...I guess my stomach just feels like butterflies in the stomach, then also my hands always just fiddle a lot, and I get sweaty. (P7)*

Communication difficulties impacted on participants' ability to communicate distress to their support system. One participant described his experience of embodied distress prior to undergoing surgery:

> *My body just goes…from, yeah, I'm fine, to, yeah, I think I'm going to be sick within seconds, like, I'm not really thinking anything. (P8)*

Developmental Delay. Participants shared their understanding of being late to talk and having difficulties making speech sounds, with an impact on relationships in the early years:

> *Oh yeah, I couldn't talk when I was younger. So, I had, like, I don't know what it's called but I had things to help me talk, I guess. (P7)*

The Burden of Diverse Medical Challenges

Substantial variability was present in the nature and extent of described medical challenges across the data. However, the emerging concepts included *regular and repeated interventions*, *physical limitations*, *experiencing pain* and *changes after surgery*.

Regular and Repeated Interventions. Participants described either an ongoing burden of interventions or significant periods of intervention in the past:

> *I've had a heart operation when I was six months old…I'll need another one, when I'm 13... (P3)*
>
> *My back, my knees. Um, two curves and scoliosis of the spine. (P8)*

The impact of these challenges ranged from difficulties around awareness of surgical decision making to distress around the procedures themselves, with a clear impact on mental health where interventions were experienced as traumatic:

> *I'm not very good with needles…and the thing is, my veins are very hard to find...because last time they had to do it in my foot...yeah [that] was very distressing. (P8)*
>
> *[The MRI Scan] was awful…When I had to go to appointments I was shaking. (P5)*

Shaking, worrying, we struggled to get him in the building. He was biting his nails and pulling his hair out. (P5 Parent).

Physical Limitations. Physical limitations, including difficulties standing due to scoliosis, hearing difficulties and tiredness due to heart problems, were well represented within the data and were understood to impact on social and educational experiences:

[PE]'s too difficult, its, and, er, they speak too quickly. (P5)

Sometimes I can't hear people up close. Mainly if it's quite loud...Sometimes I miss words out. (P6)

Experiencing Pain. Pain was also a common factor linked to physical limitations and medical procedures, with an impact on concentration and engagement with activities. This is illustrated in the description of one participant attending school prior to spinal surgery:

My back was killing me and my legs and everything…And [the spinal brace] didn't help because whenever I was breathing it was pushing on my lungs and hurting me. (P9)

Changes After Surgery. Experiences of the impact of changes after surgery were variable, but present across the data. A common theme was the impact of cleft palate surgeries, which improved speech and therefore confidence around communication:

I could eat and swallow and stuff but one of [the operations] quite helped because I would chew in my cheek, which was quite painful. (P2)

It felt a bit weird at the start and then you get used to it, and then it was better...My talking's a bit better. Sometimes it's still hard to say tricky words. (P10)

However, the mental load of being involved in decision making and the unknown outcome of surgeries was also evident, and participants often expressed ambivalence around surgical outcomes:

I was like, do I want to do [the surgery] or do I not want to do it. Because it's basically just ruined my football because I was, that's what I enjoyed doing…I could do that before and now I can't, and it's just ruined it. (P9)

Navigating Education

Several points of difficulty emerged connected to participants' experiences of education. The primary concepts included *academic difficulties*, *specific executive functioning difficulties*, *the school environment*, and *a non-responsive system*.

Academic Difficulties. The impact of 22q11DS on general academic ability was also evident and linked with both neurodevelopment and participants' *feeling different*:

At school, like, with English. It's, like, difficult. Like, very complicated…It's very hard…Like with poems, and with language. I just get them mixed up. (P2)

Where additional support was offered, this was valued by participants:

Sometimes it's hard for me, like, to read out loud and that sort of stuff. But, we've got, like, teachers that scribe you. (P10)

However, experiences of shame and distress also emerged in relation to having visible additional support within a mainstream setting. Finding the right environment for the child therefore presented as an important factor in supporting learning. The following quote relates to bullying experienced in a mainstream primary setting in the context of a child with additional support in place, and demonstrates a link between navigating education and peer relationships:

I was embarrassed about being helped...I felt stupid…They said I was stupid. I didn't like some of them. (P5)

Specific Executive Functioning Difficulties. A dominant theme in the experience of education was a difference in the ability to attend to salient information, plan, organise and

switch between modes. The need for these skills increases in the secondary education environment, with transition to secondary often presenting additional challenges:

> *I thought I had one teacher, every day. For all the lessons. And then to have different ones for every lesson, I was like, what am I doing right now? I was very weirded out [laughter]. This teacher and that teacher. (P2)*

These additional challenges were often discussed in the context of increasing anxiety in secondary education:

> *In primary school I didn't actually find that many things difficult. Because I didn't like maths, I still found maths difficult, but I didn't worry about it…I just went along and did it. (P7)*

The School Environment. The school environment presented several challenges. Changes in the environment, such as rule changes or rules that were perceived as being applied inequitably, presented challenges and one property that linked these experiences was a more rigid thinking style:

> *I'm not allowed to listen to music…which I find really annoying because in year 7 I could but now I can't. (P4)*
>
> *Yeah, the rules. When they change them, not knowing the rules. (P10)*

Similarly, this quote illustrates the mental load of changes in the environment:

> *It's difficult, like, because when we got back to school from Easter, it was all different…There was a girl, a place to put bags in the girls' toilets…And it's all gone now because they're changing things and it's all different. (P10)*

The school environment also presented sensory challenges, including sensitivity to noise and sensitivity to clothing:

> *I've got quite sensitive ears. So, if things, cause, like, with house assemblies and things...It's quite noisy and I don't really like it. (P4)*

Not, like, itchy school shirts. I have to wear my blazer. I hate the blazers, it's so annoying. (P7)

The experience of these challenges linked with feelings of difference and contributed to both anxiety and avoidance of school:

[School] makes my brain hurt. It's too confusing for it. (P9)

A Non-Responsive System. Ideas about school not being responsive to participants' needs also emerged. Participants tended to respond to this with ambivalence. Here, a participant describes the response to his request to be moved into a class with one of his peers, after he had been separated from primary school friends:

They said, "we'll see", and they said, "we'll talk to you." And it's been, how many months since September? And they haven't said anything. (P3)

Navigating Peer Relationships

The category *navigating peer relationships* developed from several concepts, including *peer relationship difficulties*, *barriers to forming relationships* and *social environmental challenges*.

Peer Relationship Difficulties. Peer relationship difficulties were a dominant theme of participants' experiences. There were several examples of peer victimisation, many of which linked directly to 22q11DS. The below example illustrates this in a primary school context:

What did they call you? (P5 parent)

Dribbler. (P5)

They made fun of your dribbling and were very mean to you, weren't they? (P5 parent).

A common strategy in managing peer relationship difficulties was to avoid peers by spending time with teachers during break times:

I always had to, like, hang out with a teacher and that kind of thing. (P10)

We've got the gym at the minute, or it be like, "oi, Mr [teacher's name] make a cup of tea." (P8)

Another strategy involved internalising the difficulty and this was expressed as unresolved frustration:

My stomach would just feel weird. And my brain would be annoying and say stuff. Not out loud but in my head...maybe it'd just be, like, that I really don't like the other person and, like, why can't it be the other person. (P7)

Barriers to Forming Relationships. Internal and external barriers to forming relationships were described in the data. Participants described the impact of social communication difficulties on their ability to maintain relationships:

She thinks I'm avoiding her but I'm not. It's because she doesn't really talk to me...When someone talks to me, I can't stop talking. (P9)

Another barrier involved the impact of classroom management strategies to meet multiple needs in specialist settings:

The year 11 classes were being split...and what I reckon the old teachers did there was split the ones that were troubled…into a class of their own. And Mr [teacher], or whoever it was, got them. Like, the stricter teacher basically. (P8)

Social Environmental Challenges. Linking experiences of peer relationships and educational settings were challenges specific to the social environment. Participants experienced difficulties with other children disrupting the environment and difficulties in resolving social conflicts:

I find it quite irritating if they're, like, really pushy with things. And they disrupt the class and things. It just bugs me... when they, like, call out in class. (P4)

Sometimes it's a bit tricky, because, like, if the teacher just writes something down everyone talks again and it gets a bit tricky to concentrate. (P10)

Feeling Different

The model demonstrates how the categories of education, medical challenges and peer relationships relate to one another and influence the category, *feeling different*. This comprises several experiences which were grouped under the concept's *sibling difficulties, experiencing 22q11DS, experiences of diagnosis* and *sensing differences from peers*.

Sibling Difficulties. Sibling difficulties were a prominent theme within the data, comprising the common experiences of tension with siblings, difficulties resolving conflict and having a lack of shared interests. The support system and scaffolding of sibling relationships was an important factor in how conflict was experienced. Here, a participant describes incidents leading to conflict with siblings:

Oh, being rude or anything like that, not listening, them being rude or me being rude or [sibling's name] freaking out...That kind of thing really. (P8)

So yeah, they don't get on really. They all clash. (Parent of P8)

Experiencing 22q11DS. Participants' experiences of 22q11DS were expressed in terms of the rarity of the condition and not knowing anyone else with 22q11DS. This linked with participants' own understanding of the condition and the extent to which they felt impacted by it:

Nobody else I know at my school has 22q. I mean, I don't really understand that much, apart from it's to do with your DNA and things. (P4)

I'm not really sure how to describe it. I guess I think differently. (P7)

Ideas about 22q11DS were related to both diagnosis and the way that the condition was discussed within the child's system.

Experiences of Diagnosis. Differences were observed in the way participants talked about 22q11DS based on how much dialogue about 22q11DS there had been within the young person's system. Participants' who reported being told about the diagnosis later in childhood spoke quite tentatively about their understanding of the condition:

I don't know when I got diagnosed with it. But my parents told me, like, a month before I left primary school…We talked about it for, like, the first couple of days, when my mum and dad told me. But we haven't really talked about it that much. (P4)

This contrasted with the way 22q11DS was talked about by participants who had been made aware of their diagnosis at an earlier age. These descriptions were more confident and linked to positive understandings of the condition:

I was the first one to get 22q in our entire family tree…we say, "it's just one of those things." (P3)

I've known about it for basically my whole life. (P6)

I understand that some people have it, and I'm not alone. (P10)

Sensing Differences from Peers. Another point of connection between participants' experiences of education, peer relationships and feeling different was the way in which difference from peers presented across these domains. For example, in the process of attempting to meet the educational needs of the young person, systems sometimes functioned to separate participants from their peers:

When I started [at school], all my friends got separated from me to their own form. And, um, I just started on my own. (P3)

So, he's in a nurture form, aren't you? He's in a form with a slightly smaller group." (Parent of P3).

Separation from peers was described as a central cause of distress:

And if [she] feels isolated it quickly causes extreme distress. (Parent of P7).

Participants also described a desire to connect with peers who had similar experiences to them, to mitigate feelings of difference and connect with others:

Sometimes I want to, like, go on Facebook and join the group…Sometimes I say to my mum that I want to be like my friends and that kind of stuff. (P10)

The Power of a Responsive Support System

Multiple participants described the presence of a supportive system, which often included parents and school staff. Concepts included *developing supportive attachments*, *managing physical limitations* and *experiences of NHS support*.

Developing Supportive Attachments. The availability of supportive attachments was seen as a significant resource for the young person:

There's a teacher who handles things quite well that I like. (P4)

The presence of supportive friendships was also significant, for participants who had been able to develop these relationships, often with adult support:

If I get upset, I want [my friends] to give me a hug. Because if I get sad, I get, like, my friends make me laugh all of a sudden and I just get happy again. (P10)

Academic support from both parents and teachers was key to participants' feeling they were managing well:

I would speak to my favourite STA who I've known since year 7. Because…she understands how I feel so I can talk to her. (P10)

Managing Physical Limitations. Support from the child's system in managing physical limitations was also seen as important for wellbeing, given the impact of pain on participants' experiences:

Limit the walking. That kinda thing. PE's probably lighter than what most people would do. (P8)

Positive Experiences of NHS Support. Where individuals had accessed support from the NHS, participants spoke about this positively. The support received impacted on the overall experience of surgery and recovery, with support from speech and language staff being particularly highly valued:

The speech therapist was really helpful. I felt a bit more, like, confident. (P10)

It was really good to be fair. Really good. Er…I forgot. Yeah, they like, treated me good and it was…it was very good yeah. (P2)

The Roots of Anxiety

This category developed from 'feeling different' and encompassed a range of experiences of anxiety stemming from the environmental challenges the young person had encountered. The concepts included *separation from attachment figures, the mental health burden of experiences, the mental load of peer difficulties, worries about surgery* and *fear of the unknown*.

Attachment and Separation. Difficulties with attachment presented in the form of separation anxiety from parents, family members and pets. This theme developed from the content of interviews and observations around process, where participants often expressed concerns about separation:

What's [name] doing? (P5)

He's just asking where the other dog is. He's worried about him. (P5 parent)

Distress around separation was described by one young person in relation to school avoidance:

You would always drop me [at school] and I would have a... mental breakdown and you would take me back home. (P9)

Yeah, so, sort of, the separation part, the anxiety, the separation anxiety, was a bit much. (P9 parent)

The Mental Health Burden of Experiences. The mental health burden of experiences linked to 22q11DS was evident across many participants' experiences. This linked with experiences of education, medical challenges and peer relationships and caused disruption to participants' sleep and mental wellbeing:

> *I used to be sick on the train on the way up [to hospital]. Because I'd get so amped up. (P8)*
>
> *[The anxiety] carries on when I'm asleep because I had it last night when I fell asleep around midnight and then I woke up at 2am and couldn't sleep. (P9)*

One participant described the impact of being asked about her condition by peers. Her words illustrate the influence of feeling different and a desire to avoid conversations about 22q11DS:

> *Sometimes it affects me, like, when my friends ask me what happens and that kind of stuff. Sometimes I just don't wanna say and I feel like crying. Especially if new people join the school. But if I get to know them, I tell them what happened. (P10)*

The Mental Load of Difficulties in Peer Relationships. Participants spoke about difficulties in peer interactions, which linked feeling different and difficulties in peer relationships through individuals' appraisals of social contexts:

> *I worry a lot about partners and stuff. So there has to be certain people that I have to be with. (P7)*

Participants described reliance on teachers to help them manage anxieties around peer relationships:

> *Just silence. Lots of awkward silence…I don't know how I got over that. Er, my new teacher just kind of made me sit next to one of the boys there and I became friends with him. (P3)*

Worries About Surgery. Anxieties around medical procedures, both past and future, were also described by participants. Past medical interventions were described as anxiety provoking but manageable. Regarding future surgeries, there was a sense of avoiding focusing too much on what the surgery would be like:

I didn't like those wires that they put through your mouth and nose. It was a bit weird because you just go to sleep really quickly. (P10)

Mainly I think about what I'll get after [the surgery] …Sometimes I worry that it will hurt a bit. But I try not to think about it. (P3)

Fear of the Unknown. Many participants described uncertainty and even fear around navigating potential difficulties that may arise:

I'm mostly panicking about my grades…that I might fail some things. (P2)

I worry about if I did need an operation in the future. Because that might ruin my career, if I have one in the future. (P2)

The risks around future medical procedures were also a concern to participants who were facing significant future surgeries:

That is, genuinely [a concern], like, they said it's 0.1% but if you're drilling holes in a spine, like, yes, they do it three or four times a month, but there is still that risk, you know? (P8)

Developing a Sense of Self

The presence of a responsive support system linked into evidence of a developing a sense of self. The concepts comprising this category included *building competence, expressing creativity* and *engagement in leisure activities*.

Building Competence. Participants descriptions of their achievements enabled the development of who they were as individuals, whether this related to academic or non-academic skills:

I've got two or three [qualifications]. I've done my maths, done my science. I think two people in my class done their science but that's it really. (P8)

I quite like playing piano. I'm grade 5. (P4)

Expressing Creativity. Creativity was one of the strongest themes in the data, and this was expressed in a variety of ways, but tended to link with the identity of being a creative person:

I like doing things like Lego because it's creative and I like doing creative stuff. (P7)

I'm very creative...I mean, it's good to be able to build what you like, or when you learn to build what you like. (P8)

Engaging in Leisure Activities. Participants varied in their engagement with regular leisure activities, but leisure activities were seen as vehicles to build self-esteem:

Most of the time I enjoy doing Lego and art and crafts. And at school I enjoy doing science experiments. (P1)

I like doing things like Lego, because it's creative...I also like birds, um, I like video games, I like drawing and I like colouring stuff. (P7)

Building Independence

Building independence was another key to participants' resilience. The concepts in this category included *self-soothing* and *building peer relationships*.

Self-Soothing. The concept of self-soothing as a key skill to be built upon was present across the data and participants were often able to describe their engagement in self-soothing activities. One theme was engaging in special interests:

I want to learn more about space. I've been into space since I was, like, five...I just quite like it because it looks quite beautiful, and it makes me feel slightly relaxed. (P4)

Accessing strategies such as spending time alone or in mindful activities helped participants to manage difficulties in the week:

I do taekwondo...every Thursday and Tuesday...Mostly friends from primary school do it...I like walking there on my own. So, it's something I do by myself. (P3)

Similarly, multiple participants spoke about relationships with animals, and the positive impact these could bring:

Um, frogs. Maybe frogs...I love frogs…Frogs and chocolate. (P7)

The only thing that keeps me calm is my cat down there. (P9)

Building Peer Relationships. Building peer relationships was integral to positive experiences and this was a prominent theme in the data:

I've got quite a few people who are very important to me…they're quite nice, they're not annoying. (P4)

I like talking to [friend] because he starts conversations and we talk for another, like, hour. (P9)

Proactive Coping

Developing a sense of self and *building independence* were seen to resource CYP and enable their engagement with active coping strategies, rather than falling into avoidant behaviours. The concepts comprising this category included *preparing for changes* and *taking positive action*.

Preparing for Changes. Participants engagement in approaching changes impacted on their experiences of events and was described in a variety of ways. It represented facing change head on and feeling prepared. Important changes discussed included forthcoming surgeries, school transitions and decisions about the future. For example, while some participants were avoidant of conversations around surgery, others described engaging in discussions with family to feel part of the decision-making process. One participant described her thoughts about a potential future surgery, illustrating engagement with the decision-making process:

They did say it might happen. But I don't know when, for this. But I'm not sure if they're going to do it...but sometimes in my head I think that I want to do that operation. To keep my hand straight. (P10)

Taking Positive Action. Participants positive actions were also observed across several different areas, including persisting with school attendance despite worries, having a positive attitude and engaging in therapy where it has been offered:

Oh yeah. I'm [at school] every single day. (P7)

I just tend to get on with things. (P6)

I have this thing called 'life skills'… And I also do art therapy. (P7)

Discussion

Overview of Findings

The aims of the current study were to identify which aspects of life were identified as stressful by CYP with 22q11DS and which strategies and supports were drawn upon by participants to manage their experiences. In doing so, we aimed to build a model of stress and coping that would have resonance with existing knowledge in adjacent areas of research (Nelson, 2017).

The beginnings of the model drew on existing theories of neurodevelopment, which suggest that genetic vulnerabilities interact with environmental factors, to influence development and increase the risk of various conditions (Calvete et al., 2014; Walker et al., 2008). Neurodevelopmental difficulties were found to impact on CYP with 22q11DS in a variety of ways, including the ability to communicate distress.

The model then provided evidence that children with 22q11DS face adverse experiences from early childhood that are both linked to the syndrome and can have a wide-reaching impact across the contexts of education, peer relationships and managing health challenges. This supported existing theorising around adverse experiences that CYP with

22q11DS may face (Beaton & Simon, 2010), as well as evidence that adolescents with 22q11DS experience higher levels of perceived stress in daily life than typically developing peers (Ilen et al., 2023).

The finding that experiences of feeling different were influenced by both stressors and the power of a responsive support system links with findings in the post-traumatic stress research, that positive relationships act as a buffer to stressful experiences (Wang et al., 2021). CYP's support systems influenced their ability to apply active coping strategies, an important finding when considered in the context of evidence that resilience and coping modify the physiological effects of stress in both individuals with 22q11DS and typically developing peers (Armando et al., 2018; Schiele et al., 2020). A support network comprising family, education and health staff scaffolded CYP to engage in active coping across different contexts.

The finding that anxieties emerged from adverse experiences and contributed to avoidant coping in CYP with 22q11DS supports existing theories around the role of intolerance of uncertainty in the maintenance of anxiety in the general population (Birrell et al., 2011). CYP with 22q11DS described experiencing uncertainty about the future, relating to both academic difficulties and the potential need for future surgical interventions. There was variability in the extent to which individuals demonstrated avoidant or active coping in discussing these challenges.

Strengths and Limitations

There were several strengths to the study. To the best of our knowledge this was the first qualitative piece of research to examine the experiences of CYP with 22q11DS with a view to developing a theoretical understanding of experiences of stress and coping. Our findings demonstrate that it is possible to gather rich data from CYP with 22q11DS using qualitative methods, despite the anticipated social communication challenges. A further

strength was that participants were recruited from both clinical and community sources, meaning that our sample was more likely to be representative of the children in the general 22q11DS population.

Limitations included the fact that theoretical sampling of participants was not possible due to the relatively small pool of potential participants. The online format of interviews may also have impacted on the richness of data, although this was necessary for practical purposes, since participants were recruited from a wide geographical area. The nature and scope of the study also prevented us from representing a developmental course within the model, which shows how the relationships between categories may change over time as children develop through adolescence.

Qualitative research does not seek to be generalisable or provide causal explanations, but to have explanatory power and resonance with existing theory. There was significant variability between the experiences of individuals participating in the study across areas such as medical interventions and experiences of schooling, which was anticipated from our scoping literature search. However, there was sufficient depth within each of the categories for the findings to be informative in understanding the potential challenges faced by CYP with 22q11DS. There was also resonance with qualitative data emerging from the only other existing study involving CYP with 22q11DS, for example, in the area of presenting educational challenges (Wray et al., 2021).

Clinical and Research Implications

Our findings suggest there are several gaps in current educational and healthcare provisions for CYP with 22q11DS. In educational settings, CYP have highlighted that their needs are not well understood and that experiences across the domains of physical needs, educational needs and peer relationships can have wide reaching effects that reverberate throughout the contexts of the individual's life. This research recognises the experiences that

CYP with 22q11DS can have where settings have a poor understanding of their difficulties. School staff should be mindful that CYP may have difficulties in expressing distress and should be proactive in addressing problems even in the absence of overt manifestations of distress.

Clinical and Educational Psychologists working in healthcare should also be mindful of the impact of managing complex health conditions on CYP, and their experiences of stress across health, educational and peer contexts. The focus of interventions should be on strengthening the child's network and coping strategies. The finding that sibling difficulties contributed to children with 22q11DS feeling different suggests a role for family therapy in managing difficulties.

Our findings demonstrate that it is possible to speak directly with CYP with 22q11DS about their experiences and their needs, and that communication barriers can be overcome to gain valuable insights. Although qualitative research does not seek to be replicable, the theoretical understandings of the experiences of CYP with 22q11DS developed in this research could be tested in further qualitative research, such as thematic analyses. The findings of this study could also be used to develop further research questions that may be addressed quantitively. For example, the effectiveness of Education Health and Care Plans or school school or community based psychological interventions for children with 22q11DS in improving social or educational outcomes. The evaluation of interventions aimed at reducing stress and augmenting coping skills would also be an appropriate area of research in the 22q11DS field.

Conclusion

This study used a modified grounded theory methodology to investigate stress and coping in ten CYP aged 10-15, and to develop an explanatory theoretical model. Ten related categories emerged, including neurodevelopmental difficulties, the burden of diverse medical

and physical challenges, navigating education, navigating peer relationships, feeling different, the power of a responsive support system, the roots of anxiety, developing a sense of self, building independence and proactive coping. A structural model illustrated the interrelationships between categories in the model.

My findings suggest that children and young people with 22q11DS experience multiple stressors emerging from educational, healthcare and peer contexts and these experiences can have a significant impact on CYP's lives. The presence of supportive relationships impacted on children's ability to build a sense of self, develop independence, and engage in proactive coping. The model also considers the impact of anxiety and avoidance on children's experiences.

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Appendices

Appendix A: Detailed Quality Scores of Included Studies

Checklist	Albert et al., 2018	Antshel et al., 2014	Antshel et al., 2017	Hamsho et al., 2017	Hooper et al., 2013	Maeder et al., 2016	Taylor et al., 2018	Van den Heuvel et al., 2018	Wagner et al., 2017	All Studies
Are the objectives/hupotheses of the study stated?	1	1	1	1	1	1	1	1	1	**9**
Is the target population defined?	1	1	1	1	1	1	1	1	1	**9**
Is the sampling frame defined?	0	1	0	0	0	0	1	0	0	**2**
Is the study population defined?	1	1	1	1	1	1	1	1	1	**9**
Are the study setting (venues) and/or geographic location stated?	1	0	1	0	0	0	1	1	0	**4**
Are the dates between which the study was conducted stated or implicit?	1	1	1	0	0	0	1	0	0	**4**
Are eligibility criteria stated?	1	1	1	1	1	1	1	1	1	**9**
Are issues of 'selection in' to the study mentioned?	0	0	0	0	0	0	1	1	0	**2**
Is the number of participants justified?	0	1	0	1	0	0	1	0	1	**4**
Are numbers meeting and not meeting the eligibility criteria stated?	0	0	0	0	0	0	0	0	0	**0**
For those not eligible, are the reasons why stated?	0	0	1	0	0	0	0	0	0	**1**
Are the numbers of people who did/did not consent to participate stated?	1	0	0	0	0	0	1	0	0	**2**
Are the reasons that people refused to consent stated?	0	0	0	0	0	0	0	0	0	**0**
Were consenters compared with nonconsenters?	0	0	0	0	0	0	1	0	0	**1**
Was the number of participants at the beginning of the study stated?	1	1	1	1	1	1	1	1	1	**9**
Were methods of data collection stated?	1	1	1	1	1	1	1	1	1	**9**
Was the realiability (repeatability) of measurement methods mentioned?	1	1	0	0	0	1	0	1	1	**5**
Was the validity (against a gold standard) of measurement methods mentioned?	1	1	0	0	0	0	0	0	1	**3**
Were there any confounders mentioned?	1	1	1	1	1	1	1	1	1	**9**
Was the number of participants at each stage specified?	0	1	1	1	0	1	1	1	1	**7**
Were reasons for loss to follow up quantified?	0	0	0	0	0	0	0	0	0	**0**
Was the missingness of data items at each wave mentioned?	0	1	1	0	0	0	0	0	1	**3**
Was the type of analyses conducted stated?	1	1	1	1	1	1	1	1	1	**9**
Were 'longitudinal' analysis methods stated?	1	1	1	1	1	1	1	1	1	**9**
Were absolute effect sizes reported?	1	1	1	1	1	1	1	1	1	**9**
Were relative effect sizes reported?	0	0	1	0	0	0	0	0	0	**1**
Was loss to follow up taken into account in the analysis?	1	1	1	1	0	0	1	1	1	**7**
Were confounders accounted for in the analysis?	1	1	1	0	1	1	1	0	1	**7**
Were missing data accounted for in the analysis?	0	0	1	0	0	0	1	0	1	**3**
Was the impact of biases assessed qualitatively?	0	1	0	1	1	0	1	1	1	**6**
Was the impact of biases estimated quantitively?	0	0	0	0	0	0	1	1	1	**3**
Did authors relate results back to target population?	1	1	1	1	1	1	1	1	1	**9**
Was there any other discussion of generalisability?	1	1	1	1	1	1	1	1	1	**9**
Score	**19**	**22**	**21**	**16**	**14**	**15**	**25**	**19**	**22**	
Percentage	**58%**	**67%**	**64%**	**48%**	**42%**	**45%**	**76%**	**58%**	**67%**	

Appendix B: Expression of Interest Form

Salomons Institute for Applied Psychology

One Meadow Road, Tunbridge Wells, Kent TN1 2YG

Ethics approval number: *322657*
Version number: 1
Participant identification number for this study:

Title of Project: An exploration of the experiences of young people who have a diagnosis of 22q11.2 deletion syndrome

Name of Researcher: Holly Ward

Expression of interest form

1. I confirm that I have been told verbally about the above study and at this point I would like to receive some more information about what would be involved in taking part. ☐

2. I understand that I am under no obligation to proceed having received this information. ☐

3. I understand that the information on this form, including my name and contact details, will be destroyed if I do not respond to communications with the researcher within six weeks, or if I communicate that I have decided not to proceed with the study. The information will not be used for any reason other than to communicate about the above study. ☐

My name:

My email address:

My telephone number:

My address:

Signature _____ **Date**_____

Appendix C: Participant Information Sheet

[redacted]

NHS

Canterbury Christ Church University

Salomons Institute for Applied Psychology
One Meadow Road, Tunbridge Wells, Kent TN1 2YG
www.canterbury.ac.uk/appliedpsychology

Information About the Research

A study examining the experiences, including coping strategies and stressors, of children and young people who have a diagnosis of 22q11.2 deletion syndrome.

Hello. My name is Holly Ward and I am a trainee clinical psychologist at Canterbury Christ Church University. I would like to invite your child to take part in a research study. Before you decide whether to agree for them to take part, it is important that you understand why the research is being done and what it would involve for your child.

Talk to others about the study if you wish.
(Part 1 tells you the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study).

What is the purpose of the study?
Very little research has been undertaken so far that looks at children and young people's own experiences of having a diagnosis of 22q11.2 deletion syndrome and how this has impacted on their lives. This study is looking specifically at what is experienced as stressful by children and young people in this group, and what coping strategies and supports are available to them. The aim of the study is to identify areas that may be of priority for future research or service provision for children and young people with this diagnosis.

Why have I been invited?
Your child has been invited to participate in this study because they are between 10-15 years old and have a diagnosis of 22q11.2 deletion syndrome and they have either accessed the [redacted] Clinic or you have self-referred into the study via your involvement with Max Appeal.

Does my child have to take part?
Your child does not have to take part in the study. It is up to you to decide together whether to join the study. If you agree to take part, I will then ask you to sign a consent form and your child will also be asked whether they agree to take part in the study.

[redacted]

Your child is free to withdraw at any time, without giving a reason. The standard of care your child receives from the [redacted] (if relevant) will not be affected in any way by their decision to take part, decline or withdraw from the study.

What will happen to my child if they take part?
If you and your child agree and they want to take part in the study, you will be contacted by the primary researcher by telephone for an initial conversation about the research and to set up a meeting date and time. Both you and your child are welcome to attend this meeting. Your child will be asked to participate in an online interview via Microsoft Teams that will last a maximum of one hour. We recognise that people who participate in research are often interested in the outcome of the research and if this is of interest to you then you can opt to receive further information about the study by email.

Expenses and payments
If you decide to take part in the study your child will receive a £10 high street gift voucher as a thank you for participating.

What will I be asked to do?
During the interview I will be asking about experiences that are linked to your child having 22q11.2 deletion syndrome. The topics covered will include the challenges of the condition and how your child has coped with these challenges.

What are the possible disadvantages and risks of taking part?
It is possible that talking about some of these issues may be distressing for your child. Your child can decide to stop the interview at any time and there will be a debrief at the end of the interview to discuss the experience of the interview and have a conversation about whether further support is required. If further support is required the interviewer will be happy to discuss this with you further and signpost to additional support services.

What are the possible benefits of taking part?
Taking part in this research will not benefit you or your child directly. However, information generated by the research may influence the development of services and inform future research into experiences of 22q11.2 deletion syndrome diagnosis.

What if there is a problem?
Any complaint about the way you have been dealt with during the study or possible harm you or your child might suffer will be addressed. Detailed information is given on this in part 2.

Will information from or about me from taking part in the study be kept confidential?
Yes. The study will be governed by NHS ethics and legal practice and the study design and content has been granted ethical approval. All information about you and your child will be handled in confidence and any published quotes will be fully anonymised. There are some rare situations in which information would have to be shared with others. These are detailed in part 2.
This completes part 1.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

Part 2 of the information sheet

What will happen if I don't want to carry on with the study?

If you decide to withdraw prior to the interview then all data collected relating to you and your child will be erased. Given the length of the study and the methods being used, it will not be possible to erase data once it has been anonymised and integrated into the study. Your child's right to withdraw would therefore be respected but data collected up to the date of their withdrawal would be retained. If you do not wish to receive further follow up or information on the study outcome following the interview then this will be respected.

Concerns and Complaints

If there is a problem, you may wish to have a discussion with me, Holly Ward, in the first instance. My contact details are as follows: Holly Ward, h.ward352@canterbury.ac.uk. You can also contact me by leaving a message on the 24-hour voicemail phone number 01227 927070. Please leave a contact number and say that the message is for Holly Ward and I will get back to you as soon as possible. However, if you do not wish to discuss the issue directly with me, you may contact the Lead Supervisor to this study, Dr Kathryn Stevenson, kathryn.stevenson@canterbury.ac.uk or the Chief Investigator to the study, Dr Ruth Garcia-Rodriguez, ruth.garcia-rodriguez[redacted] If you remain dissatisfied and wish to complain formally, you can do this by contacting Dr Fergal Jones, Clinical Psychology Programme Research Director, Salomons Institute for Applied Psychology fergal.jones@canterbury.ac.uk. For any concerns or complaints regarding your personal data, you may contact the data protection officer for Canterbury Christ Church University, dp.officer@canterbury.ac.uk.

You may also discuss concerns or complaints with the PALS Service, who can be contacted using the information below:

Patient Advice and Liaison Officer (Pals)

[redacted]

Will information from or about me from taking part in the study be kept confidential?

If you and your child decide together that they will take part in the study then you will be asked to sign a consent form, and at this point your child will be allocated a participant number. This information will be kept confidentially and in paper form. The online interview will be recorded and transcribed, and the recording will be permanently deleted as soon as it has been transcribed. Transcriptions will be anonymised and held under the participant number, rather than the name. All identifying details, including the area that you live in, clinics attended, names, and other identifying features, will be omitted from the transcripts. The transcripts will not be published in full but will be kept on an encrypted USB stick in a locked cupboard in the university building for a period of 10 years following the study. Only authorised persons such as researchers, regulatory authorities and Research & Development Audit (for monitoring of the quality of research) will have access to this data.

Limits to Confidentiality

The only time when I would be obliged to pass on information from you to a third party would be if, as a result of something you or your child told me, I were to become concerned about your safety or the safety of your child or someone else.

Who is sponsoring and funding the research?
The research is being undertaken as part of Holly Ward's Clinical Psychology doctoral training and is sponsored by Canterbury Christ Church University.

Who has reviewed the study?
All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the NHS Research Ethics Committee, Wales REC6.

Further information and contact details
If you would like to speak to me and find out more about the study, or have questions about it answered, you can leave a message for me on a 24 hour voicemail phone line at 01227 927070. Please say that the message is for Holly Ward and leave a contact number so that I can get back to you. Alternatively you can email me at h.ward352@canterbury.ac.uk or Dr Garcia-rodriguez at ruth.garcia-rodriguez[redacted]. If you have any queries or concerns during the study, you can contact Holly on [redacted]

If you would like to talk further to someone about whether you should take part in the research, you are welcome to discuss this with others.

Appendix D: Easy Read Participant Information Sheet

[redacted]

NHS

Canterbury Christ Church University

Salomons Institute for Applied Psychology
One Meadow Road, Tunbridge Wells, Kent TN1 2YG
www.canterbury.ac.uk/appliedpsychology

Information

Interviewing young people who have 22q about their lives. Thinking about things that have worked well and things that have been hard.

Hello.

My name is Holly Ward.

I am training to be a Clinical Psychologist.

Would you like to take part in a research study?

I will be talking to young people who are age 10-15 and have 22q.

This leaflet is to tell you more about the study so that you can decide if you would like to take part.

Why have I been invited?

You have been invited to take part because you have 22q.

[redacted]

We have contacted your parents because you have been to the [redacted] Clinic, or know people at Max Appeal.

Do I have to take part?

No. It is your choice.

If you decide to take part, you can also change your mind and decide not to later on. You don't need to say why.

What will happen if I take part?

If you agree, I will arrange to meet you online.

We will chat about how things are going. I might ask you about what you're good at and about friends and school. I might also ask about how you found out you had 22q. We might talk about doctor's appointments, or other things that have happened that you think are important.

You don't have to talk about anything you don't want to. You can say that you don't want to answer.

We will talk again afterwards, when you have had time to think about how the interview went. You can tell me other things you have remembered, or ask me questions if you would like.

What if I feel upset?

Sometimes talking about things can be hard. You can decide to stop the interview if you want to.

I can also give you some numbers to text, with people who can help, if you're having difficult feelings.

You can have a parent in the interview if you like.

What might the research be good for?

This research will help people to understand what it can be like to grow up with 22q.

It will help others to know about people with 22q and their strengths. It will also tell people about some challenges and difficulties that people with 22q can face.

Confidentiality

What you say will be between you and me. I might write about your words, but I won't let people know your name.

If you say something that makes me worry about your safety, I will have to share that with your parent or the person responsible for you. This would be if you say that you might hurt yourself or someone else, or that someone has hurt you.

Appendix E: Consent Form

00

Canterbury Christ Church University

Salomons Institute for Applied Psychology
One Meadow Road, Tunbridge Wells, Kent TN1 2YG
www.canterbury.ac.uk/appliedpsychology

CONSENT FORM

Title of Project: A study examining the experiences, including coping strategies and stressors, of children and young people who have a diagnosis of 22q11.2 deletion syndrome

Name of Researcher: Holly Ward

Participant Identification number for this study:

Please initial box

1. I confirm that I have read and understand the information sheet dated 1st September 2023 (version 3) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my child's participation is voluntary and that they are free to withdraw at any time without giving any reason, without their medical care or legal rights being affected. ☐

3. I understand that data collected during the study may be looked at by the supervisors to the projects, Dr Kathryn Stevenson and Dr Ruth Garcia-Rodriguez, and by the consultant to the project, Dr Jeanne Wolstencroft. I give permission for these individuals to have access to my child's anonymised interview transcripts. ☐

4. I agree that anonymous quotes from my child's interview and other anonymous data may be used in published reports of the study findings. ☐

5. I agree for my child to take place in the above study, subject to their assent. ☐

Name of Participant_____ **Date**_____

Signature of parent/guardian _____

Name of Person taking consent _____ **Date**_____

Signature _____

IRAS Study Reference: 322657

OPTIONAL

I agree to be contacted by the research team to receive a copy of the paper resulting from this study.

I would prefer to be contacted by (please check the box):

Email ☐ via this email address: _____

Telephone ☐ via this number: _____

Signature: _____

Appendix F: Assent Form

[redacted]

Canterbury Christ Church University

Salomons Institute for Applied Psychology
One Meadow Road, Tunbridge Wells, Kent TN1 2YG
www.canterbury.ac.uk/appliedpsychology

ASSENT FORM

Title of Project: A study examining the experiences, including coping strategies and stressors, of children and young people who have a diagnosis of 22q11.2 deletion syndrome

Name of Researcher: Holly Ward

Participant Identification number for this study:

Please initial box

1. I have read and understand the Easy Read Information sheet dated 17th July 2022 (version 1) for the above study. I have been able to ask questions and my questions have been answered. ☐

2. I understand that I do not have to answer every question asked. If I do decide to be interviewed, I can change my mind about this either before or during the interview. I will not have to give a reason for this. ☐

3. After the interview is finished, I understand that what I have said will be used in the project. I will be offered a phone call with Holly Ward to check she has understood what I said and that I am ok. ☐

4. I know that some things I say might be printed in the study but that my name will not be used. ☐

5. I agree to be in the study. ☐

My Name _____ **Date**_____

Holly Ward (my interviewer) Signature _____ **Date**_____

Appendix G: Initial Interview Schedule

Canterbury Christ Church University

Salomons Institute for Applied Psychology

One Meadow Road, Tunbridge Wells, Kent TN1 2YG

Proposed Interview Schedule

Confirm the young person's assent to participate in the research
Review limits to confidentiality

Develop a Genogram (map) of Family and Peer Relationships (rapport building)
Open discussion around how important relationships have developed and where support has been found.

Are there any difficulties that you have had?
Potential prompts (home, school, medically).
How did you feel when those things happened?
How did you cope and move forward?

Diagnosis
How did you find out that you had 22q11?
What happened around that time (if remembered)?
(If remembered) How did your family cope, and support you at that time?
(If remembered) Was there anyone else who helped you around being diagnosed?

Potential Medical Stressors
What has your experience been with 22q11?
Can you tell me in what ways it has affected you (if any)?
How have you coped with those things?

Social Care and other support
Have you had any support from outside of the NHS?
How has that been?

School Experience?
Do you get help at school?
What has your experience of school been so far – are there good things or bad things that have stood out?

Closing
Experience of the Interview?
Thank you & next steps

Appendix H: Health Research Authority Approval

This document has been removed from the electronic copy.

Appendix I: Approval from NHS Research Department

This document has been removed from the electronic copy.

Appendix J: Abridged Research Journal

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Appendix K: Extracts of Initial Coding

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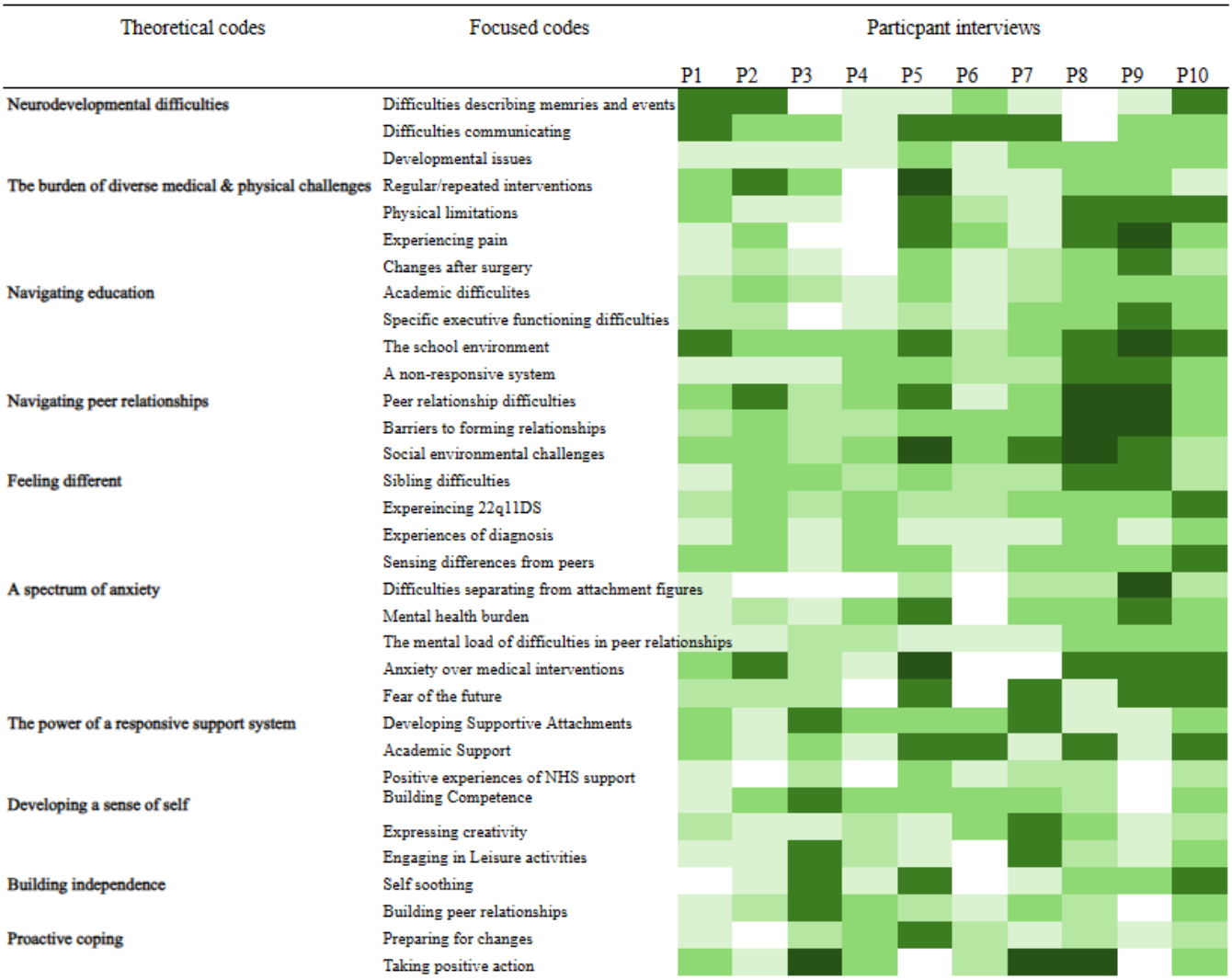
Appendix L: Extracts of Selective Coding

This document has been removed from the electronic copy.

Appendix M: Conceptual Depth Table (Showing the Presence of Categories and Concepts Across Participants)



Note: This table describes the range and complexity of the categories and concepts that emerged from the data. The darker shade represents the theme presenting more times within the interview.

Appendix N: End of Study Summary Report for Ethics Committee

IRAS Project ID 322657
Canterbury Christ Church University
[redacted] Hospital (NHS Site)

Health & Care Research Wales
[redacted]

I am writing to inform you that the above study has now ended, and to provide you with a summary of the findings.

A qualitative, modified grounded theory methodology was applied to the project. Ten children and young people (aged 10-15) with 22q11.2 deletion syndrome were recruited through [redacted] Hospital and Max Appeal (a National 22q11.2 deletion syndrome Charity). Interviews were transcribed and encoded, and a theoretical model was developed.

Analysis led to the development of a theoretical model with ten related categories. The categories included neurodevelopmental difficulties, the burden of diverse medical and physical challenges, navigating education, navigating peer relationships, feeling different, the power of a responsive support system, the roots of anxiety, developing a sense of self, building independence and proactive coping. A structural model illustrates the interrelationships between categories in the model and a copy of this model is attached.

Our findings suggest that children and young people with 22q11DS experience multiple stressors linked to educational, healthcare and in peer relationship contexts and that these experiences can have a wide-reaching impact across different areas of the child's life. Furthermore, experiences in these domains can lead to children feeling different from peers. The presence of supportive relationships was found to have an impact on children's ability to build a sense of self, develop independence and engage in proactive coping strategies. The model also considers the impact of anxiety and avoidance on children's experiences.

The research study will now be closed, and the End of Study Form will be completed within the IRAS system.

Kind regards,

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