Long-term Mental Health and Multimorbidity Outcomes in 22q11.2 Deletion Syndrome

A Comprehensive Study from Childhood to Adulthood

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ABSTRACT

22q11.2 deletion syndrome (22q11.2DS) is a genetic disorder with a markedly diverse phenotype. **Aims:** Examine mental health and multimorbidity in adults with 22q11.2DS followed prospectively from childhood/young adult age focusing on *i)* neurodevelopmental disorder (NDD) and other psychiatric conditions in adulthood; *ii)* associations between self-reported eye-contact sensitivity and face processing; *iii)* stability in cognitive functioning and link to psychosis in adulthood, and *iv)* long-term physical health outcomes. **Methods:** The study involved 79 individuals with 22q11.2DS from an original cohort of 100, first examined at ages 1-35 years and followed up after 12-23 years at ages 18-50 years, with psychiatric and neuropsychological assessments, eye-tracking examinations, and blood sampling for amino acid analysis. **Results:** High rates of NDDs, psychiatric and physical disorders were found, and multimorbidity was very common. Even though rates of psychotic disorders were high, prevalence was lower than in other studies. Individual intellectual decline was observed in some cases despite stable group performance. Regarding psychosis, a possible link to declines in full-scale intelligence quotient (IQ), particularly verbal IQ, was found. Adult functioning correlated positively with baseline IQ but negatively with psychosis. Hyperprolinemia was not associated with any NDD, or psychiatric disorder. Self-reported discomfort with eye contact may indicate social challenges.. **Conclusions:** Findings underscore the complexity of 22q11.2DS and the necessity for long-term clinical follow-up to prevent severe psychiatric morbidity, including psychosis. Coordinated multidisciplinary care is essential for providing tailored interventions to promote health and development in this population.

Keywords: 22q11.2DS, NDD, psychiatric, cognitive, physical health, eye-contact, longitudinal

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SAMMANFATTNING PÅ SVENSKA

22q11.2 deletionssyndromet (22q11.2DS) är ett genetiskt tillstånd, som orsakas av att en bit av kromosom 22 saknas. Det är det vanligaste microdeletionssyndromet och förekommer hos 1 på 2000–4000 nyfödda. Det finns troligtvis ett mörkertal eftersom kunskapen om tillståndet är begränsad. Syndromet påverkar flera organsystem och ger upphov till fysiska, intellektuella och psykiatriska problem. Samsjuklighet är mycket vanligt. Medfödda avvikelser som hjärt- och gomfel, hormonella och immunologiska störningar är vanliga. Dessutom är utvecklingsrelaterade tillstånd som autism, ADHD och intellektuell funktionsnedsättning vanligt förekommande, och det finns en ökad risk för psykiska problem såsom ångest, depression och schizofreni. Denna avhandling syftar till att undersöka utveckling och hälsa hos en grupp omfattande 79 från en ursprunglig grupp om 100 personer med 22q11.2DS, som har följts longitudinellt till vuxen ålder. Deltagarna tillsammans med en förälder bjöds in att delta i studien. Vid uppföljningen genomfördes strukturerad psykiatrisk intervju, neuropsykologiska tester och deltagare och förälder fick besvara skattningsformulär. Vidare undersöktes med Eye tracking ögonrörelser och ansiktsprocessande samt eventuella samband med upplevt obehag vid ögonkontakt. Diagnostiken baserades på den sammantagna kliniska bedömningen. Studie I visade stabilitet, i fråga om utvecklingsrelaterade tillstånd, d.v.s. de som hade autism, ADHD och intellektuell funktionsnedsättning vid T1 hade det också vid uppföljning (T2). Vidare påvisades hög förekomst av ångest, depression och psykos. Psykos var dock mindre vanligt jämfört med resultat från andra studier. Studie II visade samband mellan självrapporterat obehag vid ögonkontakt och sociala svårigheter. I studie III noterades stabil intellektuell funktion över tid på gruppnivå, men individuella försämringar förekom. Funktion i vuxen ålder var positivt kopplad till intellektuell förmåga i barndomen, men negativt kopplad till psykos. Studie IV visade hög förekomst av medfödda missbildningar som hjärtfel och gomdefekter, samt autoimmuna och hormonella sjukdomar och hörselnedsättning med flera medicinska tillstånd.

Sammanfattningsvis framkommer att gruppen med 22q11.2DS identifierad i barndom/unga år har en fortsatt psykiatrisk problematik och stödbehov. Kombinationen av psykiatrisk och medicinsk samsjuklighet visar på ett klart behov av multidisciplinär uppföljning och samordnad vård för att stödja denna grupp, vilket kräver samarbeten mellan olika professioner och samhällsinstitutioner.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Wallin, L., Gillberg, C., Fernell, E., Gillberg, C.I., Billstedt, E. Neurodevelopmental and other psychiatric disorders in 22q11.2 deletion syndrome from childhood to adult age: Prospective longitudinal study of 100 individuals. *American Journal of Medical Genetics, part C*, 2023, 193:2, 172-182.

II. Galazka, M.A., Wallin, L., Thorsson, M., Gillberg, C., Billstedt, E., Hadjikhani, N., Åhsberg Johnels, J. Self-reported eye-contact sensitivity and face processing in chromosome 22q11.2 deletion syndrome. *Journal of Clinical and Experimental Neuropsychology*, 2023, 45:6, 570-578

III. Wallin, L., Gillberg, C., Fernell, E., Gillberg, C.I., Billstedt, E. 22q11.2 Deletion Syndrome: intellectual, visuomotor and adaptive functioning followed longitudinally. *Submitted.*

IV. Wallin, L., Gillberg, C., Fernell, E., Billstedt, E. Long-Term Health Outcomes in 22q11.2 Deletion Syndrome: Adult Physical Disorders and Phenotypic Diversity. *Manuscript*

CONTENTS

ABBREVIATIONS

22q11.2DS	22q11.2 deletion syndrome
ACDH	Adult Congenital Heart Disease
ADHD	Attention Deficit Hyperactivity Disorder
ASEBA	Achenbach System of Empirically Based Assessment
ASD	Autism Spectrum Disorder
BIF	Borderline Intellectual Functioning
CBCL	Child Behavior Checklist
CD	Conduct Disorder
CHD	Congenital Heart Disease
CMA	Chromosomal Microarray Analysis
CNC	Child Neuropsychiatry Clinic
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DQ	Developmental Quotient
EF	Executive Function
FISH	Fluorescence in Situ Hybridization
FSIQ	Full Scale Intelligence Quotient
FTF	Five-To-Fifteen questionnaire
GAD	Generalized Anxiety Disorder

GAF	Global Assessment of Functioning
GQ	General Quotient
GUCH	Grown-Up Congenital Heart Disease
IBD	Inflammatory Bowel Disease
ICBB	International Consortium on Brain and Behavior
ID	Intellectual Disability
IGRT	Immunoglobulin Replacement Therapy
IQ	Intelligence Quotient
ITP	Idiopathic Thrombocytopenic Purpura
LCR	Low Copy Repeats
MDD	Major Depressive Disorder
M.I.N.I	Mini International Neuropsychiatric Interview
MLPA	Multiple Ligation-dependent Probe Amplification
NDD	Neuro-Developmental Disorder
NGS	Next Generation Sequencing
NVLD	Non-Verbal Learning Disability
OCD	Obsessive Compulsive Disorder
P.A.R.I.S	Paris Autism Research International Sibpair study
PCC	Primary Care Clinic
PIQ	Performance Intelligence Quotient
POI	Perceptual Organization Index
PRI	Perceptual Reasoning Index
PSI	Processing Speed Index

SNRI	Selective Serotonin and Noradrenaline Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
VABS	Vineland Adaptive Behavior Scales
VCFS	Velo Cardiofacial Syndrome
VCI	Verbal Comprehension Index
VIQ	Verbal Intelligence Quotient
VMI	Visuomotor Integration
VPI	Velo Pharyngeal Impairment
WAIS	Weschler Adult Intelligence Scale
WISC-III	Weschler Intelligence Scale for Children, Third Edition
WISC-IV	Weschler Intelligence Scale for Children, Fourth Edition
WMI	Working Memory Index

1 INTRODUCTION

1.1 22Q11.2 DELETION SYNDROME

The 22q11.2 deletion syndrome (22q11.2DS) was first described in 1965 as DiGeorge syndrome, named after the American pediatrician Angelo DiGeorge, who initially identified the condition including thymic hypoplasia, hypoparathyroidism with hypocalcemia and cardiac anomalies. In 1978, American speech specialist Robert Sprintzen characterized a similar condition known as velocardiofacial syndrome (VCFS). Later, in the early 1990s, studies utilizing Fluorescence in Situ Hybridization (FISH) discovered that DiGeorge syndrome, VCFS, and several other related conditions were most commonly caused by the 22q11.2 deletion, indicating that they are, in fact, the same syndrome (McDonald-McGinn et al., 2015). At times, the acronym CATCH 22 has been used to describe this syndrome, which stands for: C for Cardiac defects, A for Anomalous facial features, T for Thymic hypoplasia, C for Cleft palate, and H for Hypocalcemia. Today, 22q11.2DS is the internationally recognized term for this condition.

22q11.2DS is the most common microdeletion syndrome, affecting approximately 1 in 2,000 to 4,000 live births (Oskarsdottir et al., 2004) , with likely many undiagnosed cases due to limited awareness of the condition among clinicians. The syndrome presents with a highly variable phenotype, affecting multiple organs and functions of varying severity, with congenital as well as later onset conditions (Bassett et al., 2005).

Most research has focused on children and adolescents; however, studies on adults with 22q11.2DS are lacking. This study explores long-term outcomes on mental health, including NDDs, multimorbidity and overall functioning in a cohort of 100 individuals with 22q11.2DS followed from childhood/young age to adulthood.

1.2 PREVALENCE

A multi-center study identified the 22q11.2 deletion in 1 in 992 fetuses (Grati et al., 2015), which is a higher prevalence than the estimated occurrence of

22q11.2DS, which was 1 in 2000 to 4000 births (Blagojevic et al., 2021; Oskarsdottir et al., 2004). In Sweden, approximately 45 children are born with this syndrome each year (*The National Board Health and Welfare*, 2023). Limited awareness and potentially mild symptoms may lead to undetected cases of the syndrome

1.3 GENETICS

The condition is caused by a deletion of a small segment on the long arm of one of the two chromosomes 22. This chromosome contains specific regions of DNA known as low copy repeats (LCRs), which are nearly identical. This similarity makes these areas, termed LCRA, LCRB, LCRC and LCRD, particularly susceptible to meiotic errors, resulting in either a loss of chromosomal material (deletion) or an excess of chromosomal material (duplication).

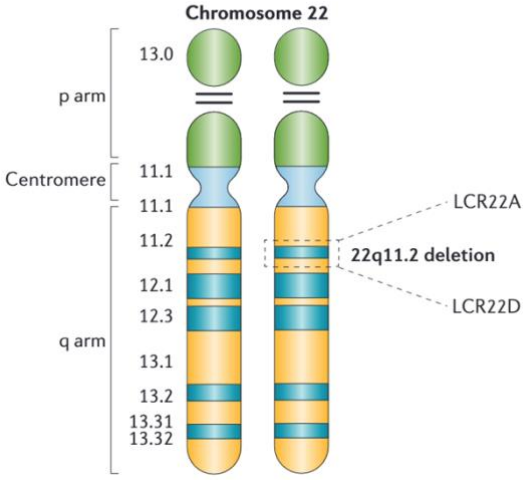

Figure 1 Deletion of a segment of chromosome 22, located at band 11.2 on the long q arm of one chromosome., adapted with permission from McDonald-McGinn, D., Sullivan, K., Marino, B. et al. 22q11.2 deletion syndrome. Nat Rev Dis Primers ***1****, 15071 (2015).* *https://doi.org/10.1038/nrdp.2015.71*

The most common deletion, in individuals with 22q11.2DS, affects approximately 85-90% of cases. This deletion spans about 2.5 to 3 million base pairs, from LCRA to LCRD, and involves around 50 genes located on one of the two chromosomes 22s. In some cases, often inherited, smaller deletions between LCRB to LCRD and LCRC to LCRD lead to similar symptoms, typically of milder severity, when compared to the proximal deletion between LCRA and LCRB, which has a phenotype more like that of the LCRA to LCRD deletion. While the absence of one copy of a gene generally does not cause significant problems, deletions of certain genes can result in a range of symptoms with varying degrees of severity (McDonald-McGinn et al., 2015; Swillen & McDonald-McGinn, 2015). Notably, the microdeletion syndrome known as distal 22q11.2DS, which spans from LCRD to LCRH and affects other genes, results in a distinct clinical expression that is different from that of 22q11.2DS (Busse et al., 2011; Mikhail et al., 2014).

Most deletions, >90%, are de novo spontaneous mutations, with neither parent affected (McDonald-McGinn et al., 2001). In almost 10 %, the deletion is found in a parent, with a slight maternal dominance (Delio et al., 2013). Haploinsufficiency in 22q11.2DS, means that roughly half of the children of an affected parent will inherit the deletion. No correlation has been found between deletion size and clinical symptoms (Michaelovsky et al., 2012; Rozas et al., 2019), making timely individual assessments essential for determining appropriate treatment, adaptations and support.

Most genes within the 22q11.2 deletion region are expressed in the brain implying that multiple genes might be implicated in the neurodevelopmental and neuropsychiatric phenotypes (Gothelf et al., 2013; Guna et al., 2015).

TBX1, a crucial transcription factor, plays a key role in 22q11.2DS, by influencing palate, cardiovascular, parathyroid, and thymic development (Du et al., 2019). It is also implicated in brain microvascular development, potentially contributing to cognitive and behavioral deficits (Cioffi et al., 2014; Paylor et al., 2006).

The COMT gene encodes catechol-O-methyltransferase, an enzyme that degrades catecholamines such as dopamine. Approximately 50% reduced activity of the enzyme has been found in individuals with 22q11.2DS (Gothelf et al., 2014). While a COMT gene polymorphism produces high-activity (Val) and low-activity (Met) enzyme versions, studies show no significant

association between this polymorphism and cognitive function or psychosis risk in 22q11.2DS (Bassett et al., 2007; Gothelf et al., 2014) .

The PRODH gene encodes proline dehydrogenase, an enzyme responsible for proline metabolism, Deficiency in PRODH activity results in hyperprolinemia, where severe forms may cause intellectual disability and seizures Elevated proline levels are observed in about 50% of individuals with 22q11.2DS (da Silva Alves et al., 2011; Squarcione et al., 2013).

1.4 DIAGNOSTICS

Diagnosis of 22q11.2DSis confirmed through genetic analysis of a blood sample. The most used techniques today are chromosomal microarray analysis or Multiple Ligation-dependent Probe Amplification (MLPA). Chromosomal Microarray Analysis (CMA) provides a comprehensive analysis of the entire genome, detecting deletions or duplications while also offering information on deletion size and any clinically relevant genome-wide copy number variations. In contrast, MLPA is a targeted analysis method, similar to FISH, which can be employed when a specific deletion or duplication is suspected. These are common methods for detecting 22q11.2 deletions but have limitations. FISH probes typically target only the proximal 22q11.2 region and cannot detect the size of the deletion or deletions outside that region. MLPA probes cover a slightly larger region, allowing determination of deletion size, but doesn't analyze the full spectrum of possible alterations. Additionally, diagnosis can also be validated using Next Generation Sequencing (NGS) technology. NGS examines all coding regions through whole exome sequencing or the entire genome with whole genome sequencing (Boot 2023).

In our cohort, diagnosis of 22q11.2DS was confirmed via FISH, a technique using fluorescently labelled DNA or RNA probes that bind to specific DNA sequences on a chromosome. This binding causes the targeted region to fluoresce, allowing visualization under a specialized microscope.

1.5 CLINICAL PRESENTATIONS

The 22q11.2DS presents a highly variable clinical spectrum, ranging from mild, barely detectable symptoms to much more pronounced manifestations affecting multiple organ systems and functions (Figure 2). Symptoms can include a wide array of congenital defects as well as medical, neurodevelopmental and psychiatric conditions that may emerge later in life, with multimorbidity being common. Additionally, symptoms and functional capabilities can fluctuate throughout an individual's lifespan.

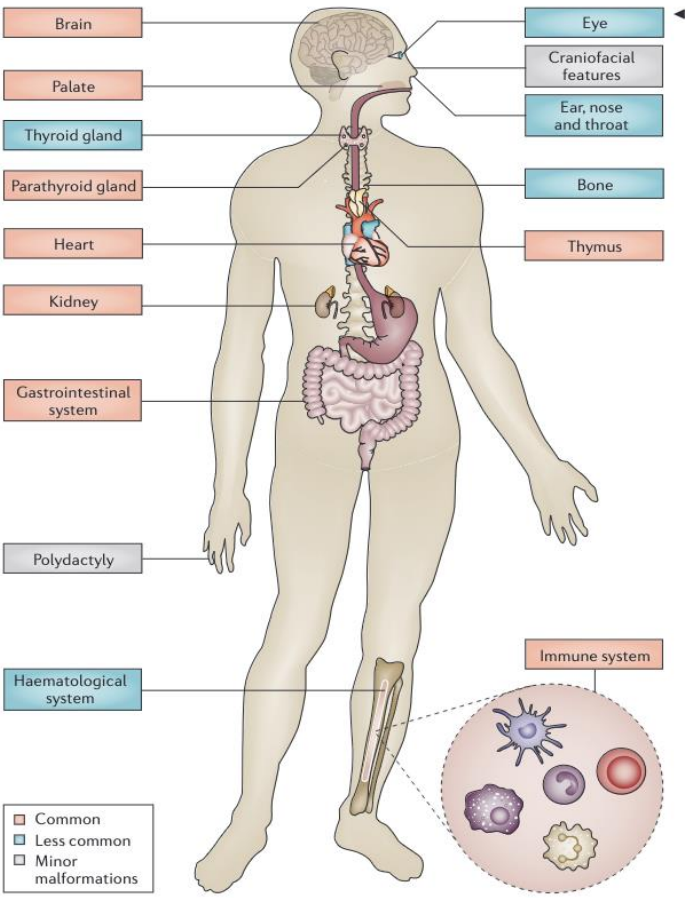

*Figure 2. Overview of the diverse organ and systems affected in 22q11.2 deletion syndrome, adapted with permission from McDonald-McGinn, D., Sullivan, K., Marino, B. et al. 22q11.2 deletion syndrome. Nat Rev Dis Primers **1**, 15071 (2015). https://doi.org/10.1038/nrdp.2015.71*

1.5.1 PHYSICAL DISORDERS

Physical disorders in 22q11.2DS commonly diagnosed in childhood include congenital heart disease (CHD), particularly conotruncal anomalies, velopharyngeal insufficiency (VPI) and thymus hypoplasia, which may lead to immune disorders such as immune deficiency and autoimmunity (Boot et al., 2023).

Mutations in the transcription factor gene TBX1 are involved in the developmental abnormalities characteristic of 22q11.2DS, specifically affecting the palate, cardiovascular system, parathyroid glands and thymus (Jerome & Papaioannou, 2001). TBX1 also plays a crucial role in brain microvascular development, potentially contributing to cognitive and behavioral impairments (Paylor et al., 2006). Defects in TBX1-mediated morphogenesis disrupt the normal development of pharyngeal arch derivatives such as the craniofacial structures, parathyroid glands, thymus, aortic arch, and cardiac outflow tract, structures originating from all three primary germ layers (endoderm, mesoderm, and ectoderm) and neural crest cells stemming from the closing neural tube (McDonald-McGinn et al., 2015).

VPI of varying degrees is present in approximately 90% of individuals. This can lead to feeding difficulties and regurgitation. Speech is also affected, leading to hypernasality and articulation problems. Even with prior surgical intervention, many adults with 22q11.2DS continue to experience velopharyngeal impairment and hypernasality. Another common structural feature of 22q11.2DS is conductive hearing loss, yet some individuals also experience sensorineural loss (Persson et al., 2012).

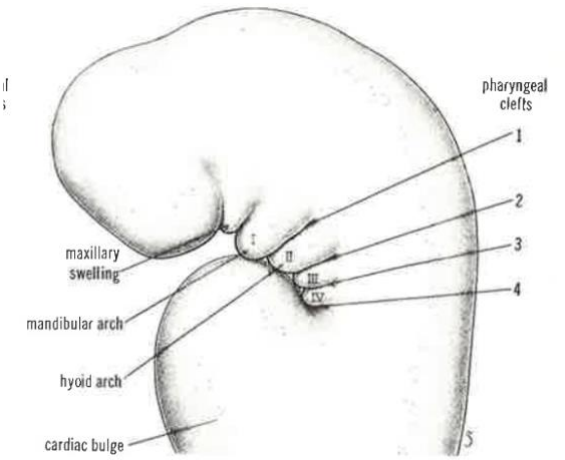

Figure 3a: The pharyngeal arches and clefts in 5-week embryo. Cardiac neural crest cells migrating from the hindbrain interact with pharyngeal endoderm to form the thymus and parathyroid glands. TBX1, a T-box transcription factor, plays a crucial role in pharyngeal surface ectoderm signaling. These cells further interact with core mesoderm in pharyngeal arches, contributing to outflow tract smooth muscle remodeling.

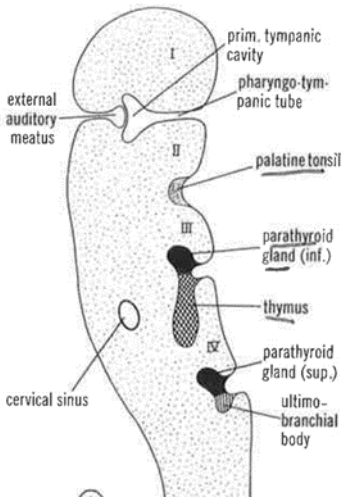

Figure 3b: Development of the pharyngeal clefts to craniofacial structures, parathyroid tissue, and thymus. With permission from Medical embryology, Jan Langman, 2nd Ed. 1969: pages 241 and 244.

Deficiencies in the development of the parathyroid glands can lead to hypocalcemia, which has a lifetime prevalence of 80% and may occur or recur at any age. The risk of hypocalcemia increases with biological stress, and in some cases; conditions such as hypomagnesemia and hypothyroidism can also contribute (Cheung et al., 2014). Hypocalcemia can be asymptomatic, but may manifest as fatigue, irritability, abnormal involuntary movements, or a prolonged QT interval. If left untreated, hypocalcemia carries a risk of severe consequences such as seizures, cardiac arrhythmias and, over time, an increased risk of osteoporosis. Guidelines recommend regular monitoring of calcium, parathyroid hormone, magnesium, thyroid stimulating hormone and creatinine levels, as well as targeted calcium monitoring in vulnerable situations such as infection, trauma, surgery, and childbirth (Boot et al., 2023).

Approximately 60-80% of individuals with 22q11.2 deletion syndrome have cardiac defects. The most common of these involve the conotruncal outflow tract, and include tetralogy of Fallot, truncus arteriosus, (figure 4a and b), and interrupted aortic arch type B. Other frequent cardiac defects are ventricular septal defect with or without pulmonalis atresia (Goldmuntz et al., 2024). Most CHDs need surgical interventions early in life and long-term specialized medical follow up at Adult Congenital Heart Disease (ACDH) clinics (Unolt et al., 2018).

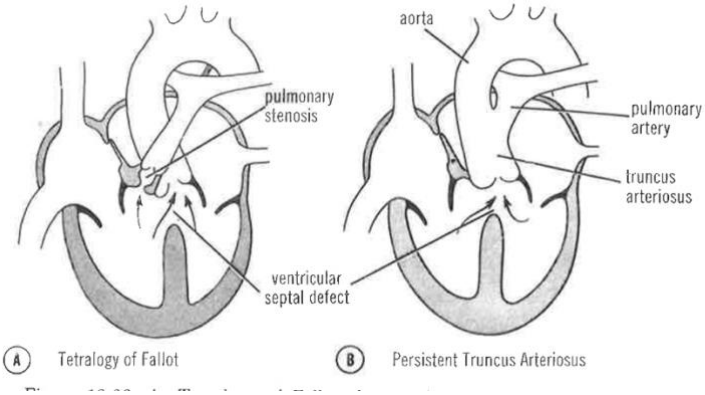

Figure 4a: Tetralogy of Fallot, characterized by pulmonary stenosis, overriding aorta, ventricular septal defect, and right ventricular hypertrophy. Figure 4b: Persistent truncus arteriosus, showing the pulmonary artery arising from the common truncus. Adapted from Medical embryology, Jan Langman, 2nd Ed. 1969: page 208

Thymic hypoplasia, common in 22q11.2DS, can result in T-cell deficiencies. In cases of thymus aplasia, infants are born with very low or absent T-cell levels, resulting in a profound immunodeficiency, significantly increasing the risk of life-threatening infections. This severe form, affecting approximately 1% of newborns with 22q11.2DS, is often detected through newborn screening for severe immunodeficiency. T-cells are also essential in regulating the immune system. A deficiency of these cells can lead to a range of complications such as increased susceptibility to chronic infections, impaired humoral immune responses, which in turn may cause impaired responses to vaccines, and an increased risk of developing autoimmune disorders. Common autoimmune disorders associated with 22q11.2DS are immune thrombocytopenic purpura, autoimmune hemolytic anemia, thyroid disorders and autoimmune enteropathies, particularly celiac disease (Mustillo et al., 2023).

In addition to hypoparathyroidism, other endocrine manifestations are hypothyroidism observed in up to 44%, hyperthyroidism in 8 %, and obesity (BMI $\geq$ 30) was observed in 38% of adults with 22q11.2DS (Soubry et al., 2024), alongside growth hormone deficiency and short stature (Weinzimer, 2001).

Gastrointestinal (GI) problems are common, even though symptoms often improve from childhood to adulthood. GI problems include chronic constipation, gastroesophageal reflux disease and functional abdominal pain (Kotcher et al., 2022). Autoimmune enteropathies such as inflammatory bowel disease and celiac disease are about 10 times more frequent in 22q11.2DS, than the general population (Ng et al., 2017; Singh et al., 2018).

Urogenital anomalies have been observed in up to 30-40% of individuals with 22q11.2DS. Ultrasound of the kidneys and bladder, a thorough medical history, and non-surgical treatments are recommended for any identified kidney or bladder problems. (Van Batavia et al., 2019; Wu et al., 2002).

Scoliosis is a common clinical feature, with a reported 20-fold increased risk, present in almost half of individuals with 22q11.2DS. Other orthopedic problems are musculoskeletal pain and recurrent patellar dislocation (Homans et al., 2019). Neurological disorders associated with 22q11.2DS are movement disorders, seizures and a higher occurrence of early-onset Parkinson's disease (Butcher et al., 2013). Of important concern are also dental health problems,

such as enamel and tooth anomalies and reduced saliva excretion increasing risk of caries (Klingberg et al., 2007).

Hyperprolinemia may disturb glutamatergic transmission (Raux et al., 2007) and severe hyperprolinemia (plasma-proline > 550 μmol/L) has been associated with an increased risk of neurodevelopmental and psychiatric disorders (Clelland et al., 2011; Raux et al., 2007), nevertheless a systematic review (Namavar et al., 2021) did not find any significant relationship between specific psychiatric disorders and hyperprolinemia.

1.5.2 NEURODEVELOPMENTAL DISORDERS

Brain expression of the majority of genes within the 22q11.2 deletion region suggests that many genes may contribute to neurodevelopmental and neuropsychiatric conditions (Gothelf et al., 2013).

Individuals with 22q11.2DS exhibit significantly higher rates of NDDs, including (ASD, ADHD, and ID, compared to the general population (Niklasson et al., 2001, 2009; Swillen & McDonald-McGinn, 2015; Swillen et al., 2018).

A large multicenter study (Schneider et al., 2014) of 1,402 individuals with 22q11.2DS (ages 6–68) reports an ADHD prevalence of approximately 40% in children, and a prevalence of ASD of 27% in adolescents. While ASD and ADHD prevalences are typically lower in adulthood in 22q11.2DS, the rates remain elevated compared to the general population. In our cohort of 100 individuals with 22q11.2DS, mean age 11 years, 44% exhibited ASD and/or ADHD, and 51% presented with ID at baseline (T1). Critically, only one-third of the participants had no NDD (Niklasson et al., 2009). Further research is needed to determine the long-term stability of these disorders, particularly in adulthood.

1.5.2.1 EYE-CONTACT DISCOMFORT AND FACE PROCESSING

Similar to individuals with ASD, ADHD, psychotic syndromes, or social anxiety disorder (SAD), individuals with 22q11.2DS often exhibit social skill impairments (Shashi et al., 2012). Eye-tracking studies of individuals with 22q11.2DS reveal atypical facial scanning, particularly reduced gaze directed at the eyes (Campbell et al., 2010; Glaser et al., 2010), which may negatively influence emotional processing and social functioning (Franchini et al., 2016). Usually, the brain has a right-sided specialization for faces, which is reflected by a preference to gaze to the left side of the face, the so-called Left-Visual-

Field (LVF) bias (Gilbert & Bakan, 1973; Harrison & Strother, 2021). Typical social-brain development relies on appropriate facial scanning, including a preference for eye gaze, and lateralization (Grossmann & Johnson, 2007; Meng et al., 2012). Avoidance of eye contact has been suggested to negatively influence development of the face processing systems (Hadjikhani et al., 2018). Research shows substantial individual variability in eye gaze patterns in 22q11.2DS. An eye-tracking study (Campbell et al., 2010) showed that individuals with 22q11.2DS displayed greater variability in eye gaze patterns than other groups.

Existing research shows that individuals with intellectual and communication disorders can describe their discomfort with, and coping strategies for, eye contact (Andréen et al., 2021; Ridley et al., 2022) This highlights the value of triangulating qualitative and quantitative data for greater validity and credibility, potentially improving our understanding of decreased eye gaze in 22q11.2DS.

Disparities in self-reported distress with eye contact could help explain many of the diverse neurodevelopmental and psychiatric conditions seen in 22q11.2DS. This could potentially identify a marker for specific behavioral and psychiatric vulnerabilities. Differences in self-reported discomfort with eye contact may contribute to the heterogeneity of neurodevelopmental and psychiatric conditions commonly seen in 22q11.2 deletion syndrome

1.5.3 PSYCHIATRIC DISORDERS

Psychiatric disorders are common in 22q11.2DS, with frequencies generally increasing with age (Kates et al., 2019). Many studies on psychiatric phenotypes in 22q11.2DS have used relatively small samples. To address this limitation, the International Consortium on Brain and Behavior (ICBB) in 22q11.2DS assembled research groups from North America, Europe, Australia, and the Middle East to pool data. This collaborative effort yielded a comprehensive description of lifetime prevalence and comorbidity patterns of neurodevelopmental and psychiatric disorders in 1,402 individuals with 22q11.2DS, ages 6 to 36+ (Schneider et al., 2014).

Anxiety disorders, slightly more prevalent in females, were common across all ages, affecting approximately one-third of children and adolescents and about one-fourth of adults. Generalized anxiety disorder (GAD) and social phobia were the most frequent anxiety types, but panic disorder was also commonly observed in adults with the condition (Fung et al., 2010; Schneider et al., 2014).

Obsessive Compulsive Disorder (OCD) was estimated to be twice as prevalent in individuals with 22q11.2DS compared to the general population (Gothelf et al., 2004; Schneider et al., 2014).

Rates of mood disorders increased significantly with age in individuals with 22q11.2DS, although bipolar disorder prevalence appeared similar to that of the general population. Mood disorders were overrepresented in females, consistent with what is found in the general population (Fung et al., 2015; Schneider et al., 2014).

Prevalence of substance use and conduct disorders was relatively low in 22q11.2DS, compared to the higher rates observed for other psychiatric conditions (Schneider et al., 2014; Vingerhoets et al., 2019).

Psychotic disorders, though feared, are not the most common psychiatric conditions in individuals with 22q11.2DS (Karas et al., 2014). The elevated risk of psychotic disorders in 22q11.2DS has been noted since the 1990s. Early studies reported a 25-fold increased risk (Green et al., 2009) compared to the general population's 0.7% lifetime risk (McGrath et al., 2008). However, a Danish population-based register study found a relatively lower, 7-fold, increased risk of schizophrenia and related psychotic disorders in 22q11.2DS (Hoeffding et al., 2017). Despite these reports of high rates of psychotic disorders, the question remains whether subthreshold psychotic symptoms reliably predict later psychosis in 22q11.2DS. Many individuals with these symptoms do not progress to psychosis, but instead develop other psychiatric disorders, such as mood or anxiety disorders (Lin et al., 2015).

Psychotic disorders are characterized by a decline in functioning, social withdrawal, and psychotic symptoms (*Diagnostic and Statistical Manual of Mental Disorders. 5th ed*, 2013). A review of longitudinal and cross-sectional studies (Tang & Gur, 2018) found that individuals with 22q11.2DS who developed psychosis demonstrated lower baseline cognitive functioning, including lower FSIQ scores and subsequent cognitive decline. These individuals also exhibited differences in brain volume. Furthermore, higher baseline psychosis-spectrum symptoms, along with comorbid dysphoric mood and anxiety, were associated with a greater risk of developing psychosis. Importantly, the study suggested that the progression to clinically significant psychosis and the age of onset in 22q11.2DS were similar to those seen in individuals at risk for psychosis without the deletion.

1.5.3.1 LINKS BETWEEN NDDS AND OTHER PSYCHIATRIC DISORDERS

Social-communication difficulties are observed in both ASD and psychotic disorders, and some suggest that ASD traits might precede the onset of psychosis (Ghaziuddin & Ghaziuddin, 2020; Kincaid et al., 2017). However, research has not demonstrated a link between autistic symptoms in childhood and psychotic disorders in adulthood (Fiksinski et al., 2017; Vorstman et al., 2013).

Individuals with 22q11.2DS and subthreshold psychotic symptoms exhibited more inattentive ADHD symptoms than individuals without the deletion, and those with a family history of psychosis. (Niarchou et al., 2018). A strong association was found between childhood inattentive ADHD and the emergence of psychotic symptoms. However, association between childhood inattentive ADHD and the development of psychotic disorders during adolescence was weaker. The authors concluded that the presence of inattentive symptoms, regardless of previous changes, predicted the emergence of psychotic symptoms (Niarchou et al., 2019).

While individuals with ID generally have increased rates of psychopathology, studies suggest that 22q11.2DS carries an independent, elevated risk, even after considering IQ. Assessments revealed significantly higher rates of ADHD, ASD, anxiety and mood disorders in 22q11.2DS compared to individuals with idiopathic ID and IQ-matched controls. There was correlation between increased psychopathology rates and low IQ in 22q11.2DS (Baker & Skuse, 2005; Fiksinski et al., 2018).

1.5.4 NEUROPSYCHOLOGY

Individuals with 22q11.2DS frequently exhibit a range of difficulties, including significant executive function impairments (e.g., flexibility, concentration, planning, initiation, problem-solving, impulse control, visuospatial function, and working memory). Arithmetic skills tend to be weaker, while reading skills appear more robust (Bearden et al., 2001; Chow et al., 2006; De Smedt et al., 2009). Moreover, speech and language delays, often accompanied by cognitive and social communication difficulties, are common and often persist across the lifespan (Solot et al., 2019). Specific language impairments in 22q11.2DS include reading comprehension, expressive language, and receptive language (Solot et al., 2001).

1.5.4.1 COGNITIVE/INTELLECTUAL FUNCTIONING

The complex neuropsychological profile of 22q11.2DS significantly impacts daily functioning and quality of life. Individuals with 22q11.2DS frequently exhibit intellectual impairment, typically falling within the borderline intellectual functioning (BIF) range (FSIQ 70-84) or mild ID range (FSIQ 51-69), centered around a mean IQ of approximately 70. More severe ID is less common (Antshel et al., 2008; Bassett et al., 2005; Chow et al., 2006; Niklasson & Gillberg, 2010; van Amelsvoort et al., 2004). A recent retrospective Dutch study of 250 adults (ages 16-69) with 22q11.2DS found 56% with ID, predominantly mild ID. Only 7% performed within the average range (FSIQ 85-115), and 36% with BIF (Vingerhoets et al., 2024).

Lower VIQ and impaired reading skills during childhood have been associated with an increased risk of developing a psychotic disorder during adolescence or early adulthood (Antshel et al., 2017; Gothelf, Feinstein, et al., 2007; Kates et al., 2019).

A study examining sex differences in cognitive function in 22q11.2DS compared 50 boys and 40 girls with the deletion to 41 "typically developing" boys and 36 "typically developing" girls. Neuropsychological assessment indicated greater cognitive impairment in boys with 22q11.2DS. Furthermore, cognitive function was negatively correlated with age in girls with 22q11.2DS. Neuroimaging data revealed a larger frontal lobe volume in boys than in girls, consistent with findings from the general population. The authors hypothesized that, while girls with 22q11.2DS might initially exhibit less pronounced cognitive impairment, this advantage might not persist throughout their lifespan (Antshel, AbdulSabur, et al., 2005).

1.5.4.2 UNEVEN IQ PROFILE

Learning difficulties are common irrespective of intellectual level. Studies have reported visual perceptual deficits, often resulting in higher verbal IQ (VIQ) compared to performance IQ (PIQ), often referred to as "uneven IQ profile" or non-verbal learning disability (NVLD) (Moss et al., 1999; Niklasson & Gillberg, 2010; Swillen et al., 1997; Woodin et al., 2001). This cognitive profile has been suggested to be more significant in childhood compared to in adolescence and adulthood (Antshel et al., 2008; Green et al., 2009).

Few longitudinal studies have investigated the stability of IQ or "uneven IQ profiles" in 22q11.2DS (Fiksinski et al., 2022). Studies examining intellectual

stability during childhood have yielded inconsistent results. Some studies report declines of up to 10 IQ points, predominantly verbal skills, whereas non-verbal and spatial abilities seem more stable (S. N. Duijff et al., 2012; Tobia et al., 2018; Vorstman et al., 2015). Others report no significant cognitive decline (Antshel et al., 2014; Kates et al., 2019). Longitudinal data on intellectual stability from childhood to adulthood is even more limited, but research suggests a decline in VIQ with age (Gothelf, Penniman, et al., 2007; Green et al., 2009).

Verbal ability decline in individuals with 22q11.2DS has been linked to the development of psychotic disorders (Vorstman et al., 2015), although a systematic review found inconsistent evidence for a direct link between VIQ decline and psychosis (Jhawar et al., 2021). However, unlike anxiety and depressive disorders, a clear association between lower intellectual function and psychosis in 22q11.2DS has been demonstrated (Schneider, Schaer, et al., 2014). Verbal declines itself has also been identified as a potential predictor of psychotic episodes in this population (Vorstman et al., 2015).

1.5.4.3 STABILITY OF INTELLECTUAL FUNCTIONING

Longitudinal studies of individuals with 22q11.2DS show a negative correlation between age and intellectual function, in particular a decline in VIQ. This suggests that some individuals experience a gradual cognitive decline as they age (Gothelf, Penniman, et al., 2007; Green et al., 2009). Studies show variability in cognitive paths across the lifespan among individuals with 22q11.2DS (S. N. Duijff et al., 2012; Green et al., 2009) emphasizing that intellectual ability may not remain stable throughout life (Chawner et al., 2017; Swillen & McDonald-McGinn, 2015). While IQ is commonly regarded stable in typically developing youth, a study of 388 individuals (ages 8-24) with 22q11.2DS, showed a mean decline of 7 FSIQ points, and 9 VIQ points (Vorstman et al., 2015). Critically, the decline was steeper in those who developed a psychotic disorder. Nevertheless, some individuals with 22q11.2DS do experience intellectual improvements over time.

Cognitive decline during childhood in individuals at risk for psychosis, often accompanied by neuropsychological deficits, may increase the risk of later-onset psychosis (Kates et al., 2015; Pontillo et al., 2019; Vorstman et al., 2015).

A review of cross-sectional and longitudinal studies on individuals with 22q11.2DS (Tang & Gur, 2018) revealed that those who developed psychosis

had lower baseline cognitive functioning, including lower FSIQ scores, subsequent cognitive decline and altered brain volume. Higher baseline psychotic symptoms and comorbid mood and anxiety disorders were also predictive factors. The authors further suggested that the transition to clinically significant psychotic disorders and the age of onset were comparable between 22q11.2DS individuals at clinical psychosis risk without the deletion.

The increased risk of early-onset neurodegenerative disorders, such as Parkinson's disease also may have an impact on cognitive decline in 22q11.2DS ((Boot et al., 2023; Butcher et al., 2013).

1.5.4.4 VISUOMOTOR INTEGRATION FUNCTIONING

Individuals with 22q11.2DS often exhibit motor and coordination difficulties, impacting gross and fine motor control, eye-hand coordination, and handwriting. (Niklasson & Gillberg, 2010; Roizen et al., 2010; Van Aken et al., 2007). Van Aken et al. found that children with 22q11.2DS scored lower than typically developing, IQ- and age-matched controls on visual perception and motor coordination subtests of the Beery visuomotor integration (VMI) (Van Aken et al., 2009). This implies that these VMI deficits are not solely attributable to general developmental delays but may be specific to 22q11.2DS. A study of 65 five-year-old children with 22q11.2DS examined the relationship between intellectual function and VMI skills. Results showed a significant correlation between FSIQ, and visual perceptual skills assessed by the VMI. However, motor coordination skills within the VMI assessment did not demonstrate a significant correlation with FSIQ, suggesting that motor coordination difficulties do not significantly impact intellectual functioning at this age (S. Duijff et al., 2012). VMI impairments, affecting both visual perception and motor coordination, are considered risk factors for academic difficulties (Carames et al., 2022). Furthermore, deficits in visuomotor processing may influence social cognition and contribute to the development of psychotic disorders (Lu et al., 2021).

VMI difficulties were evident in our 22q11.2DS group at time point 1 (T1). Unlike “typically developing” children, where performance IQ (PIQ) and VMI scores are correlated, our group showed lower VMI scores compared to PIQ at T1. This discrepancy may stem from VMI's higher demands on fine motor skills compared with many PIQ subtests. Learning disabilities were observed more frequently than ASD or ADHD (Niklasson & Gillberg, 2010).

1.5.4.5 ADAPTIVE FUNCTIONING

Adaptive functioning is the ability to adjust to and cope with the demands of daily life. It comprises skills like self-care, home living, communication, social skills, community participation, self-direction, education, work, leisure, and health and safety. Adaptive skills vary considerably in individuals with 22q11.2DS (Butcher et al., 2012; Fiksinski et al., 2019; Leader et al., 2023). Adaptive functioning and socioeconomic status (SES) are reciprocally related; low SES negatively impacts adaptive functioning, and conversely, low adaptive functioning can hinder improved SES (Hao & Farah, 2020). A recent study of 250 individuals assessed using the Vineland Adaptive Behavior Scales (VABS), found that a majority presented with low adaptive functioning. Lower FSIQ, ASD, and male sex were associated with lower adaptive functioning (Vingerhoets et al., 2024). A history of psychotic disorder significantly predicted lower adaptive functioning, particularly in daily living skills and socialization, while factors such as congenital heart disease, anxiety/mood disorder, age and sex were not significant predictors (Butcher et al., 2012). Conversely, higher IQ and EF skills, and no psychotic illness were linked to better adaptive functioning (Butcher et al., 2012; Fiksinski et al., 2019). Furthermore, stress, sleep disorders, and fatigue negatively impact overall functioning in this population (Armando et al., 2018; Vergaelen et al., 2017; Yirmiya et al., 2020).

While many individuals with 22q11.2DS require support with tasks like completing forms, managing finances, and complex life decisions, daily living skills such as household management and employment demonstrate relative strengths(Butcher et al., 2012). A study of 138 adults with 22q11.2DS found that 33% held competitive employment, 25% held supported employment, and 41% were unemployed. (Butcher et al., 2012; Mosheva et al., 2019).

Individuals with 22q11.2DS may be more susceptible to stress and have lower resilience in managing daily stressors, including change. However, their response to stress can be unpredictable, with some adults demonstrating surprisingly successful coping mechanisms, particularly if routines and support systems remain consistent, even during difficult events like bereavement (Armando et al., 2018; Van de Woestyne et al., 2022).

1.6 PURPOSE OF THIS STUDY

While numerous studies have investigated cognitive, psychiatric and neurodevelopmental aspects of 22q11.2DS, in children and adolescents, longitudinal research tracking these aspects across the lifespan, particularly focusing on daily life functioning, is limited.

This longitudinal study follows a large sample of individuals with 22q11.2DS over many years to address this gap. Understanding the evolving cognitive, developmental and psychiatric profiles, along with daily functioning, will contribute to a broader scientific knowledge that will facilitate early recognition and diagnosis, of great importance for tailored support strategies essential to improve long-term health and quality of life. Insights from studying this population may inform research on similar conditions in the general population and may lead to new therapeutic approaches.

2 SPECIFIC AIMS

This study investigates the longitudinal trajectory of cognitive, neurodevelopmental, psychiatric, medical aspects and daily functioning in 100 individuals with 22q11.2 deletion syndrome (22q11.2DS) followed prospectively from childhood to adult age. The aims are to:

1. Estimate the prevalence of NDDs, and other psychiatric diagnoses, evaluate the stability of NDD from childhood to adult age and assess the predictive value of childhood NDDs in relation to the development of psychotic disorders in adulthood;

2. Explore the relationship between self-reported eye contact sensitivity and current neurodevelopmental and psychiatric profiles, potentially identifying a clinical marker for behavioral and psychiatric vulnerability;

3. Determine how childhood cognitive and neurodevelopmental profiles predict intellectual, psychiatric and functional outcomes in adulthood;

4. Characterize the long-term health outcomes, including physical disorders, health care utilization and describe the medical diversity in adulthood.

3 PARTICIPANTS AND METHODS

An overview of all subjects participating in the studies is presented in Table 1.

Table 1.The clinical description of the study group and methods used in study I-IV

Study	I	II	III	IV
Object of study	NDD and psychiatry	Eye contact sensitivity	Cognition	Medical health
Target group	100	100	100	100
Group examined	79	27	56	79
Attrition	21 %	73%	44%	21%
Male: female	36:43	12:15	21:35	36:43
Age (mean, SD)	28.0 (6.6)	28.4 (7.2)	27.0 (6.4)	28.0 (6.6)
GAF (mean, SD)	49 (12)	51 (10)	51 (12)	49 (12)
FSIQ (mean, SD)	68.2 (11.6)	69.9 (11.8)	68.2 (11.6)	68.2 (11.6)
ID (%) *n* = 56	51 (64)	16 (59)	36 (64)	36 (64)
ASD (%)	28 (35)	8 (30)	21 (38)	28 (35)
ADHD (%)	36 (46)	10 (37)	26 (46)	36 (46)
Methods	M.I.N.I DSM-5 WAIS-IV P.A.R.I.S GAF scale FSS-III ASRS ABCL	Eye tracking M.I.N.I DSM-5 WAIS-IV P.A.R.I.S GAF scale FSS-III	M.I.N.I DSM-5 WAIS-IV Beery VMI P.A.R.I.S GAF scale PSI FSS-III ASRS ABCL	M.I.N.I DSM-5 WAIS-IV P.A.R.I.S GAF scale PSI MHI AAA

FSIQ=Full Scale Intelligence Quotient, ID=Intellectual Disability, ASD=Autism Spectrum Disorder, ADHD=Attention Deficit Hyperactivity Disorder, NDD=Neurodevelopmental Disorders, M.I.N.I.=Mini International Neuropsychiatric Interview, DSM-5=Diagnostic and Statistical Manual of Mental Disorders, Fifth Ed., WAIS-IV=Weschler Adult Intelligence Scales, P.A.R.I.S=Paris Autism Research International Sib pair study, GAF=Global Assessment of Functioning, FSS-III=Fear Survey Schedule-III, ASRS=Adult ADHD Self-Report Scale, ABCL= Adult Behavior Checklist, TCI=Temperament and Character Inventory, Beery VMI= Beery-Buktenica Developmental Test of Visual-Motor Integration, PSI=Psychosocial Interview, MHI=Medical Health Interview, AAA=plasma-Amino Acid Analysis

3.1 PROCEDURE

3.1.1 PARTICIPANTS AT BASELINE STUDY

Original assessments (T1) were conducted at the Child Neuropsychiatry Clinic (CNC) in Gothenburg, Sweden, between 1997 and 2005 (Niklasson et al., 2001, 2002, 2005, 2009; 2010). The study included 100 individuals with confirmed 22q11.2DS (*n*=87 <18 years; 58 females and 42 males; ages 1–35 years) identified through FISH analysis. These individuals represented the first 100 consecutive cases referred from Region Västra Götaland for neuropsychiatric evaluations at the CNC.

3.1.2 PARTICIPANTS AT FOLLOW-UP

3.1.2.1 PROCEDURE FOR INCLUSION AND EXCLUSION

All participants assessed at T1 were at least 18 years old in 2016–2021 and thus eligible for follow-up. The mean follow-up period was 17.0 years (SD = 2.4; range: 12–23 years). Data collection was extended to account for the COVID-19 pandemic. Recruitment for the study was initially via letter, followed by phone calls. Once contacted, participants were invited to participate in T2 assessments, with the option of including a parent/proxy. Six participants were excluded from the T2 study: three due to relocation abroad, three due to death. Nine declined to participate, and six did were unreachable (letters, phone calls, text messages). This left 79 participants (36 male and 43 female), for the T2 follow-up (ages 18–50 years) (Figure 5). No significant baseline differences were observed in FSIQ, age, or gender between participants who completed the study and those who did not.

Studies I and IV included all 79 participants. In study II, 27 (12 male and 15 female) of the 79 were also examined using eye tracking. Study III included 56/79 participants (21 male and 35 female) who also completed the WAIS-IV; of whom 44/79 (13 male and 31 female) also underwent Beery VMI testing.

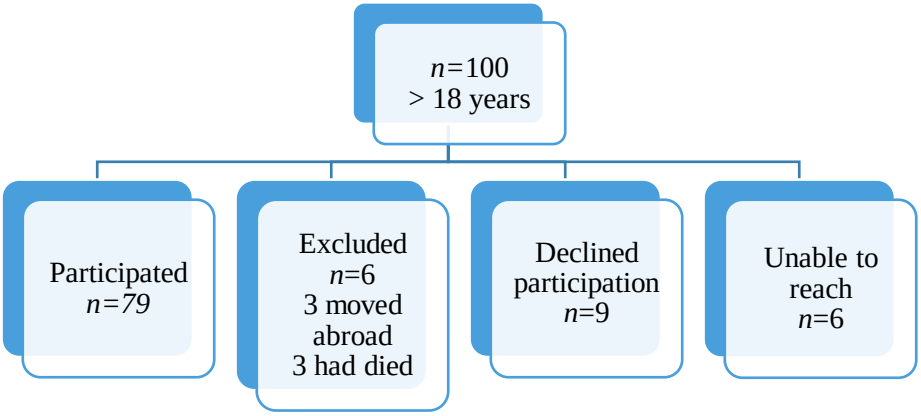

Figure 5: Flowchart demonstrating inclusion and exclusion procedure

3.1.2.2 PROCEDURE FOR COLLECTION OF DATA

No significant differences in baseline FSIQ or age were found between participants who completed the follow-up assessments and those who did not. The data collection for the majority of participants (*n*=52) took place at the research center. Home visits were carried out for those who preferred (*n*=12), and digital assessments necessitated due to the COVID-19 pandemic (*n*=9), were also used. Six participants declined individual clinical assessments to either a digital parent interview (*n*=5) or a center-based parent interview (*n*=1). Of the 79 individuals included, 56 completed WAIS testing, and 44 completed the Beery- VMI. Reasons for non-participation in the WAIS testing included: digital assessment incompatibility (*n*=9), parental rather than participant participation (*n*=6), participant exhaustion or declined participation (*n*=8), and 12 participants, having completed the WAIS, declined further participation in the VMI due to fatigue.

Study IV included 79 participants of whom amino acid analysis were performed on 34 participants (16 male, 18 female). No significant differences were found in the prevalence of NDDs, epilepsy, mood disorders, or psychotic disorders between participants who provided blood samples and those who did not. However, anxiety disorders were significantly more prevalent among those who did not provide blood samples (χ^2 (1, n = 79) = 9.72, p = .002).

3.2 INSTRUMENTS

3.2.1 MEASURES AND ASSESSMENTS AT BASELINE STUDY

3.2.1.1 NEUROPSYCHIATRIC ASSESSMENT

The T1 protocol involved detailed clinical diagnostic assessments for ADHD, ASD, ID, Tourette syndrome, OCD, and conduct disorder (CD), conducted by a child and adolescent psychiatrist or a child neurologist. This also comprised semi-structured and structured interviews and a comprehensive neuropsychological assessment.

3.2.1.2 NEUROPSYCHIATRIC DIAGNOSTIC PROCESS

Psychiatric diagnoses of ASD and ADHD were made using DSM-IV criteria(APA, 1994) by the child psychiatrist or the child neurologist, integrating data from interviews, medical evaluations, and observations. A psychologist assessed cognitive function, including developmental/intellectual level, visuomotor skills, executive functions, and mentalization/theory of mind. Intellectual disability was diagnosed based on a FSIQ or developmental quotient (DQ) of less than 70, combined with functional limitations and deficits in social adaptation. Within this ID group, mild ID was defined as an IQ between 50 and 69, moderate ID as an IQ between 35 and 49 and severe ID as an IQ below 35 (Niklasson et al., 2001, 2002, 2009; Niklasson et al., 2005).

3.2.1.3 QUESTIONNAIRES USED

Parents completed the Autism Spectrum Screening Questionnaire (Ehlers & Gillberg, 1993; Ehlers et al., 1999; Posserud et al., 2006), the Conners' Brief Parent Rating Scale (Conners et al., 1998), the Child Behavior Checklist (Tm, 1991) , and the Five to Fifteen questionnaire (FTF) (Kadesjö et al., 2004; Lambek & Trillingsgaard, 2015). Of these instruments only the FTF was used in the diagnostic process.

3.2.1.4 DEVELOPMENTAL ABILITY AND PROFILE

For the youngest children developmental functioning was assessed using the Griffiths Mental Developmental Scales for Children (n=6). These scales comprise six subscales: locomotor, personal-social, hearing and language, eye-hand coordination, performance, and practical reasoning. An overall general quotient (GQ) is calculated from the average developmental quotients across all subscales, with a mean of 100 and standard deviation of 16 (Griffiths, 1984).

3.2.1.5 INTELLECTUAL ABILITY AND PROFILE

Intellectual functioning was assessed in the remaining children and adolescents using the *i)* Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R, n=9) (Wechsler, 1990), *ii)* the Wechsler Intelligence Scale for Children–III (WISC-III, n=33) (Wechsler, 1992), and the *iii)* Wechsler Adult Intelligence Scale (WAIS, n=8) (Wechsler, 1996). Given the longitudinal design and use of multiple Wechsler scales, only verbal IQ (VIQ), performance IQ (PIQ), and full-scale IQ (FSIQ) results from T1 are reported.

Due to severe medical problems and lack of language, FSIQ could not be determined for two participants. These individuals (with clinical moderate and severe intellectual disability, respectively) were assessed using parts of the VABS. These two participants were excluded from statistical analyses.

3.2.1.6 VISUOMOTOR INTEGRATION ABILITY

Visuomotor integration was assessed using the Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI) (Beery, 2010). This test, suitable for individuals aged 2 to 100, involves copying geometric shapes in a developmental sequence using paper and pencil

3.2.2 MEASURES AND ASSESSMENTS AT FOLLOW-UP

3.2.2.1 NEUROPSYCHIATRIC ASSESSMENT

A child and adolescent psychiatrist and a clinical psychologist conducted comprehensive diagnostic evaluations of each participant's clinical, psychiatric, and neuropsychiatric status. This involved semi-structured and structured interviews, as well as a comprehensive neuropsychological assessment.

3.2.2.2 NEUROPSYCHIATRIC DIAGNOSTIC PROCESS

NDDs and psychiatric diagnoses, following DSM-5 criteria (APA, 2013), were made by the child and adolescent psychiatrist, integrating all accessible information, together with the assessments listed below, and clinical judgment. Neuropsychological assessments were primarily performed by the clinical psychologist, but for a few participants, the child and adolescent psychiatrist administered WAIS and VMI testing supervised by the clinical psychologist. In total, 56 individuals underwent IQ testing at both T1 and T2. Three participants did not complete T2 IQ testing. In these cases, diagnoses of ID were based on T1 results (n=22) or further clinical evaluation (n=2).

3.2.3 METHODS

3.2.3.1 DSM-5

The DSM-5, is a standardized classification system for mental disorders used globally in research and clinical practice (Regier et al., 2013). It defines diagnostic criteria for various mental disorders based on observable symptoms, behavioral patterns, and functional impairments..

3.2.3.2 M.I.N.I

The Mini International Neuropsychiatric Interview (M.I.N.I) is a structured diagnostic interview for major psychiatric disorders included in the DSM-5 and ICD-10 classifications. (Sheehan et al., 1998). Validation studies comparing the M.I.N.I to other structured diagnostic interviews, such as the Structured Clinical Interview for DSM-III-R (SCID-P) (Spitzer et al., 1992) and the Composite International Diagnostic Interview (CIDI), demonstrated comparable reliability and validity. Essentially, the MINI can be administered significantly faster than these alternative instruments (Sheehan et al., 1998).

3.2.3.3 P.A.R.I.S

The P.A.R.I.S (Paris Autism Research International Sibpair study) schedule, developed by our research group, includes a DSM-IV-TR diagnostic schedule to check for autistic symptoms, activity level symptoms, expressive speech development, and medical disorders (Philippe et al., 1999).

3.2.3.4 PSYCHOSOCIAL INTERVIEW

A semi-structured interview form, developed by our group, assessed participants' quality of life across various domains (Cederlund et al., 2008; Helles et al., 2017). The interview explored living status (own living with/without support, sheltered living, living with parents), social relationships (number of friends; defined as a person they consider a friend but who is not a next kin or personal assistant, romantic relationships; if they were married, lived with a partner, had a girl-/boyfriend, or if they ever had experienced a romantic relationship), employment (if yes; type of employment, regular/wage-subsided/sheltered employment), and education (degree attainment, current studies), and living situation Participants and/or their parents took part in the interview.

3.2.3.5 ASSESSMENT OF MEDICAL HEALTH

Assessment of medical diagnoses and medical treatments were established from comprehensive screening of patient records from baseline assessments

(T1) and from a structured interview at T2. This interview included a protocol developed by our research team covering developmental, psychiatric and medical history and current problems, including contacts with health care, and treatment efforts.

3.2.3.6 GLOBAL ASSESSMENT OF FUNCTIONING SCALE

The Global Assessment of Functioning (GAF) scale (*Diagnostic and Statistical Manual of Mental Disorders. 5th ed*, 2013) assess the severity of psychiatric symptoms and overall functioning across social, occupational, and psychological domains. Ranging from 0 to 100, lower scores indicate greater impairment and higher scores better functioning. The research team collaboratively rated GAF scores based on all available information. Scores between 51 and 60 indicated moderate difficulties. Scores between 41 and 50 suggested more significant problems, and scores below 40 represented severe symptoms and impairments.

3.2.4 COGNITIVE ASSESSMENT

3.2.4.1 INTELLECTUAL FUNCTIONING

The WAIS-IV, including the eight-subtest short form (Bulzacka et al., 2016; Wechsler, 2008b), was used to assess intelligence. Fifty-six participants underwent IQ testing at both T1 and T2. For three individuals who did not complete IQ testing at T2, ID diagnoses were based on T1 scores (n=22) or clinical judgment (n=2).

For practical reasons, the Verbal Comprehension Index (VCI) was estimated using the Vocabulary and Similarities subtests, and the Perceptual Reasoning Index (PRI) using Block Design and Matrix Reasoning. The WAIS-IV manual provides these estimated scores. Standard subtests for Working Memory Index (Digit Span and Arithmetic) and Processing Speed Index (Coding and Symbol Search) were also administered. An "uneven IQ profile," indicative of nonverbal learning disability (NVLD), was defined as a difference of greater than 15 points between verbal IQ (VIQ)/VCI and performance IQ (PIQ)/PRI scores derived from the Wechsler scales.

3.2.4.2 VISUOMOTOR INTEGRATION ABILITY

The Beery VMI (Beery, 1997) was used to assess visuomotor integration. This standardized test, appropriate for individuals aged 2 to 100 years, involves copying geometric shapes in a developmental sequence using paper and pencil.

Strong test-retest reliability has been demonstrated in previous studies (Harvey et al., 2017).

3.2.5 QUESTIONNAIRES USED

3.2.5.1 THE ADULT ADHD SELF-REPORT SCALE

The Adult ADHD Self-Report Scale (ASRS) (Kessler et al., 2005), a 24-item questionnaire, was completed by both parent and participant (*n*=45), by participant alone (*n*=5), or by parent alone (*n*=11). The ASRS demonstrates good psychometric properties, including high specificity and positive predictive value for ADHD (Ustun et al., 2017).

3.2.5.2 THE FEAR SURVEY SCHEDULE-III

The Fear Survey Schedule-III (Wolpe & Lang, 1964) was completed by the participants (*n*=51). This instrument assesses anxiety by evaluating fear intensity (on a five-point scale) in response to 76 situations/objects across five factors representing social anxiety, agoraphobia, fear of physical injury/death, fear of sexual/ aggressive situations, and fear of harmless animals. Responses range from "not at all disturbed" to "very much disturbed." The Fear Survey Schedule–III demonstrates established reliability and validity in various anxiety-related contexts(Blankstein et al., 1993).

3.2.5.3 OTHER INSTRUMENTS

The parent questionnaire Adult Behavior Checklist, (Achenbach, 2003), and the self-rated Temperament and Character Inventory (Cloninger et al., 1993)were completed by a parent/proxy. Results of these measures are not reported in this thesis but will be presented in forthcoming studies.

3.2.6 STUDY II - EYE TRACKING

3.2.6.1 PARTICIPANTS

Twenty-seven (12 male, 15 female; mean age = 28.4 years, SD = 7.2, age range = 18–50 years) participated in eye-tracking examinations.

3.2.6.2 ASSESSMENTS AND INSTRUMENTS

The face stimuli for eye-tracking consisted of 24 black-and-white, circularly cropped photographs of angry, happy, and neutral facial expressions (eight images each; four female and four male faces). These images were derived from the NimStim set of facial expressions (Tottenham et al., 2009) and presented against a gray background, displayed in random order. Every

stimulus was presented only once. In compliance with the NimStim dataset, only images of model #1 are presented here for illustrative purposes (see Figure 6).

Participants were asked about their experiences of eye contact. If discomfort was reported, follow-up questions explored how they typically managed it, which could be answered either by choosing some given alternatives (e.g., looking at other facial features), or with their own words describe their strategy of handling eye contact. The questions also determined if discomfort was specific to certain individuals (e.g., family, strangers, or individuals expressing strong emotions). This structured clinical examination during eye-tracking. The questions developed by our research group based on experience of people with ASD and/or social anxiety (Andréen et al., 2021) was considered suitable for investigating eye contact experiences in 22q11.2 deletion syndrome given the overlapping functional characteristics.

Diagnostic decisions, were based on DSM-5 criteria, using all available data. FSS-III was completed by 25 of the 27 participants, and the social subscale was used to assess social phobia. The GAF scale was used to evaluate the level of psychiatric symptoms and overall functioning across social, occupational, and psychological domains.

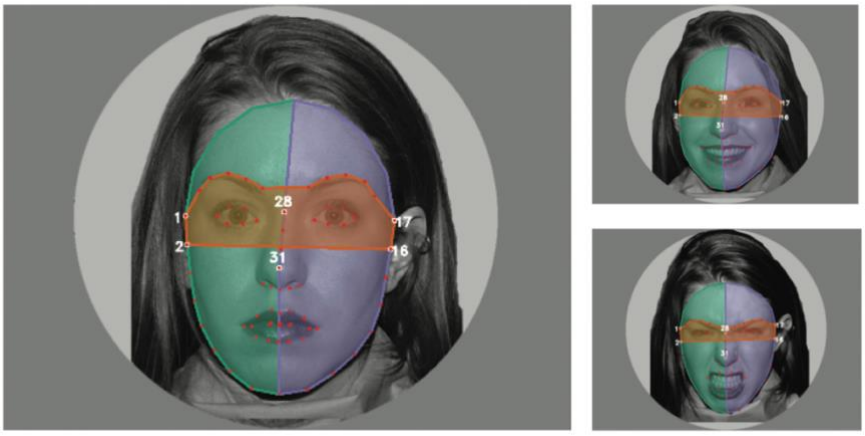

Figure 6: An example of the presented stimuli of angry (lower right), happy (upper right), and neutral (lower right) facial expressions with automatic generation of areas of interest. For each presented image, the eye area (orange) and the left (green) and right (blue) facial areas were automatically determined. Facial landmarks used for defining AOI boundaries are displayed as red points. Reprint from paper II.

3.2.6.3 PROCEDURE

Participants' eye movements were recorded at 120 Hz using a Tobii T120 eye tracker. Data acquisition was performed in a quiet testing room without natural light, with participants seated approximately 60 cm from the screen. After standard nine-point calibration, participants were instructed to freely view 24 images, presented once each in random order for 6 seconds, followed by a 15-second fixation cross. Eye tracking data, exported from iMotions version 6.4, were analyzed using Python 3.8.5 scripts. Statistical analyses and visualizations were performed in R version 4.1 using the ggstatsplot package (Patil, 2021) and SPSS version 28. Owing to the small sample size and potential outliers, non-parametric tests are reported all through the analyses.

To justify slight variations in presented images (e.g., not the same actors, minor head tilt, shift in expressed emotions), we automatically generated areas of interest (AOIs) for gaze classification. A custom Python script processed each image was processed as follows: first, a convolutional neural network approximated a rectangle enclosing the face, followed by the detection of 68 facial landmarks using an ensemble of regression trees (Kazemi & Sullivan, 2014) trained on the 300-W dataset (Sagonas et al., 2016) as implemented in Dlib (King, 2009).

Three AOIs were identified as polygons based on landmark locations. First the eye area (red area in Figure 6), included the eye-brow landmarks and the two upper cheek landmarks (see Figure 6, landmarks 1,2,16,17), and to include the forehead, a half-ellipse was estimated. The ellipse's axes were determined by the top cheek landmarks (1,17) and twice the length of the nose bridge (Figure 6, landmarks 28-31). The facial area was then split into left and right halves (Figure 6, green and blue areas).

To assess if gaze coordinates fell in the defined AOIs, a point-in-polygon problem was set up and solved by using the ray-tracing method, guaranteeing better precision than rectangle-based methods. Missing data, e.g. blinks, was categorized as outside the screen. AOIs for all 24 images were visualized and visually inspected using OpenCV (Bradski, 2000). Gaze proportion within each AOI was calculated, averaging overall trials for each participant. Trials with no more than 25% of recorded gaze on the screen were excluded (11.15% of trials). The code used in our analysis is available on GitHub at the URL https://github.com/thoraxmax/automaticAOIs.git. Following this exclusion,

participants spent an average of 84.53% of the time (range 25.38-100%) looking at the screen. Group differences in gaze on screen time were not significant based on self-reported sensitivity to eye contact (Mann–Whitney U=118, p=.18).

3.2.7 STUDY IV - ANALYSIS OF AMINO ACIDS

3.2.7.1 PARTICIPANTS

Study IV included 79 participants of whom amino acid analysis was performed on 34 participants (16 male, 18 female). No significant differences were found in the prevalence of NDDs, epilepsy, mood disorders, or psychotic disorders between participants who provided blood samples and those who did not. However, anxiety disorders were significantly more prevalent among those who did not provide blood samples (χ^2 (1, n = 79) = 9.72, p = .002, phi = 0.38).

3.2.7.2 PROCEDURE

Blood samples were collected by venipuncture using a 5/3 Lithium-Heparin vacutainer and analyzed for plasma levels of proline, glutamine, and glutamate. Samples were inverted ten times, centrifuged, and stored on ice before being frozen at −20 °C for later analysis. Plasma amino acid concentrations were determined using a standardized procedure for biological fluids. Participants were instructed to fast for at least 3 hours prior to the sample collection. Hyperprolinemia thresholds were set at 316 µmol/L for females and 377 µmol/L for males (Jacquet et al., 2005).

3.3 ANALYSIS AND STATISTICAL METHODS

3.3.1 STUDY I

Statistical analyses were performed using IBM SPSS Statistics version 28. Independent samples t-tests were employed to analyze total group data. Subgroup comparisons and analyses of dichotomous variables utilized nonparametric methods (Mann- Whitney U Test for continuous data and Fisher's exact test for categorical data). All significance tests were two-tailed, and significance level was set at $p < 0.05$.

3.3.2 STUDY II

Eye-tracking data were exported from iMotions version 6.4. Data analysis was performed using Python 3.8.5 scripts for preprocessing. Statistical analyses and visualizations were conducted in R version 4.1, leveraging the ggstatsplot package (Patil, 2021) and SPSS version 28. Considering the limited sample size and potential outliers, nonparametric tests were employed through all the analysis.

3.3.3 STUDY III

Categorical variables were analyzed using Chi-square tests. For continuous variables, Mann-Whitney U tests compared differences between sex, and Wilcoxon signed-rank tests analyzed within subject changes in IQ and VMI between timepoints. Effect sizes were calculated using Eta squared statistics. All analyses were two-tailed with a significance level of $p < .05$.

A Chi-square goodness-of-fit test compared the proportion of "uneven IQ" profiles in the 22q11.2DS group to the normative group. Pearson's correlation coefficient assessed the relationship between Full-Scale IQ (FSIQ) at T1 and T2. Linear regression was used to determine if FSIQ at T1 predicted GAF at T2, adjusting for age, sex, and psychosis. All statistical analyses were conducted using IBM SPSS Statistics version 29.0.

3.3.4 STUDY IV

Statistical analyses were performed using IBM SPSS Statistics version 29. Chi-square tests (with Yates' correction for continuity) were applied to compare frequencies and categorical variables. Nonparametric Mann-Whitney U tests compared differences between subgroups.. All tests were two-tailed, with a significance level of $p < .05$.

3.4 ETHICAL CONSIDERATIONS

All study procedures adhered to ethical guidelines of national and institutional review boards. Informed consent was obtained from parents or participants at T1, and from all participants at T2, except for three individuals with very low adaptive and cognitive functioning, for whom consent was obtained from a legal guardian. The T1 study was approved by the Research Ethics Committee

at the Faculty of Medicine, Gothenburg (reference: L604-97). The T2 study obtained ethical approval from the Regional Ethical Approval Board in Gothenburg (reference: 487-16).

4 RESULTS

4.1 STUDY I

4.1.1 PSYCHIATRIC DISORDERS AT FOLLOW UP

Major Depressive Disorder (MDD) was present in 43% (*n* = 34) of the study group, regardless of co-occurring NDDs or ID. MDD tended to be more prevalent in males (48%) than females (37%). Three participants met criteria for bipolar disorder: one with mania and two with hypomania. Six participants (4 males) reported a history of suicidal ideation.

Anxiety disorders were also common. Panic disorder (23%) and social anxiety disorder (SAD) (20%) were most common, agoraphobic disorder (13%) and generalized anxiety disorder (GAD) (11%) were also observed. Though not significant, social anxiety and GAD was more common in females. Furthermore, OCD was overrepresented (*n*=14, 18%), with roughly equal prevalence in males and females.

None of the participants were found to have symptoms of post-traumatic stress. One female participant reported a history of an eating disorder. Mild alcohol use was reported by one woman and one man. The majority of participants did not use alcohol and none reported substance use. No participants in the study group met criteria for antisocial personality disorder. Overall, no significant differences in psychiatric diagnoses were observed between males and females.

4.1.2 PSYCHOTIC SYMPTOMS

Psychotic symptoms were reported in 14% (*n* = 11) of participants. Of these, seven were females (16%) and four were males (12%). Three participants met criteria for schizophrenia spectrum disorder, including one with catatonia. Three participants had schizoaffective disorder. Three participants had experienced mood episodes with psychotic features; of whom two men had a history of recurrent depressive episodes with psychotic symptoms, and one woman had psychotic symptoms during manic or depressive episodes. Two women had experienced transient psychotic symptoms, including delusions and auditory and visual hallucinations, related to surgical procedure.

No significant difference regarding sex or age was found between those with and those without psychotic symptoms. Though not statistically significant, the group with psychotic symptoms had lower mean GAF scores at follow up, 44.0 (*SD* = 16.7) compared to 50.2 (*SD* = 10.8) in the group without psychotic symptoms (t (77) = 1.537, p = 0.298).

Participants with mood episodes and psychotic symptoms had been prescribed mood stabilizers (lithium, atypical antipsychotics, and/or antiepileptics). One of the participants with schizophrenia was prescribed antipsychotic medication, the other two were not, due to lack of efficacy and adverse effects.

4.1.2.1 NDD AT BASELINE IN THE PSYCHOTIC SYMPTOMS' SUBGROUP

ASD was significantly more prevalent (55%, n=6) in participants with psychotic symptoms at T2 compared to those without ($\chi 2$ (1, n=79) = 6.51, p = .02). No significant difference in ADHD prevalence was observed at T1 between the psychotic and non-psychotic subgroups.

4.1.3 NDD AT FOLLOW UP

ID was diagnosed in 51 of 79 participants (65%) at T2. At T2, 50 of the 79 participants (63%) had ASD and/or ADHD, of whom 14 had ASD only, 22 had ADHD only, and 14 had both ASD and ADHD. Thus, 28 participants (35%) met diagnostic criteria for ASD. The prevalence of ADHD was significantly higher in males (n = 22/36, 61%) than females (n = 14/43, 33%) (χ^2 (1) = 6.441, p = 0.011). This difference was most pronounced in the combined type and hyperactive/impulsive subtypes of ADHD. No significant difference was observed for the inattentive subtype. Stability of NDD

Of the 79 participants participating at both T1 and T2, 34 (43%) met criteria for ASD, ADHD, or both at T1. These participants had a mean GAF score at T2 of 46.5 (*SD* = 13.1), close to significantly lower than the 51.4 (*SD* = 10.8) mean GAF score for the 45 participants without ASD or ADHD at T1 (t (77) = 1.83, p = 0.07). Most individuals with T1 diagnoses of ASD or ADHD met diagnostic criteria also at T2. However, two participants with T1 diagnoses of ASD or ADHD no longer met criteria at T2. Conversely, 18 of the 45 (40%) participants without a T1 diagnosis of ASD or ADHD met criteria for these conditions by T2.

4.1.3.1 ID AT T2

Cognitive assessments were conducted at both T1 and T2 for 55 participants. Of the 27 participants with ID at T1, 21 (78%) maintained an ID diagnosis at

T2, whereas six of these 27 participants with ID at T1 showed significant improvement, with IQ scores increasing by at least 10 points and falling into the average range at T2. Conversely, 14 (50%) of the 28 participants who scored above the ID range at T1 now performed within the ID range at T2. One participant was assessed only at T2 and had an IQ below 70. Of the 23 individuals not participating in the WAIS test at T2, 22 had been IQ tested at T1 and 15 of them had been diagnosed with ID at T1, thus the probable prevalence of ID in this group is likely 65% (51/79). , Furthermore, three participants had not been IQ tested at T1 or T2, however, they were all three clinically diagnosed with ID at both assessments, suggesting that the probable rate of ID is even higher 54/79 (68%) in this group.

4.1.4 CO-OCCURRING NDDS AND PSYCHIATRIC DISORDERS

Of the 79 participants, only four (5%) did not receive a diagnosis of ASD, ADHD, or met criteria for any psychiatric diagnosis. The majority of the 75 participants with any diagnosis met criteria for more than one condition. Sixteen participants (20%) had only one condition (10 NDD, 6 other psychiatric disorders), while 59 (75%) had two or more disorders. Twenty of the 24 participants (83%) without any psychiatric disorder at T2 had ID or other NDD.

Anxiety was significantly more prevalent in the ADHD group compared to those without ADHD (t (78) = 4.484, p = 0.043). Excluding anxiety and ADHD comorbidity, no other significant relationship was found between other psychiatric disorders and NDD diagnoses.

4.2 STUDY II

4.2.1 EYE CONTACT SENSITIVITY AND FACE PROCESSING

4.2.1.1 EYE CONTACT DIFFICULTIES AND COPING STRATEGIES

Of 27 participants interviewed about eye contact discomfort, 12 (44%) reported such difficulties. Clinically, reduced eye contact was observed in 9 of these, described as "fleeing," "evasive," or "scanning" rather than "fixating". Reduced eye contact was not apparent in the remaining three. Eleven of the 12 who reported discomfort described coping strategies: four forced eye

contact, five avoided face-to-face interaction, and two used both strategies. Of these eleven participants, discomfort was reported consistently across all interactions in three, with unfamiliar people in five, and with strangers or individuals expressing strong emotions such as anger or when crying in three.

4.2.1.2 RELATIONSHIP BETWEEN PERCEIVED AND MEASURED EYE CONTACT

Eye-tracking showed that participants reporting discomfort looked significantly less at the eyes in neutral-expression stimuli. No significant difference for gaze behaviors was observed for the other emotional expressions (angry, happy), yet a trend in the same direction as for neutral faces was observed.

Participants reporting no eye-contact discomfort showed a significant left visual field (LVF) bias, looking considerably more to the left side of faces (Wilcoxon signed-rank test, W=116.0, $p < .001$, rrb = 0.93, CI95% (0.80, 0.98). This eye gaze pattern was not observed in the group reporting eye contact discomfort. In this group no bias for either side of the face was found.

Hand dominance was confirmed for 17 participants, all of them right-handed. Seventeen right-handed participants were assessed for hand dominance and eye contact comfort. Of these, five expressed discomfort with eye contact, of whom two individuals showed evidence of LVF bias. Of the 12 right-handed participants who expressed no problem with eye contact, 8 showed evidence of LVF bias.

4.2.1.3 ASSOCIATION BETWEEN REPORTED EYE CONTACT DIFFICULTIES WITH NDD AND EVERYDAY FUNCTIONING

There was no significant difference in IQ or social anxiety, measured on the social subscale FSS-III, between those who reported discomfort with eye contact and those who did not. However, participants reporting eye contact discomfort had lower levels of everyday functioning, as measured by the GAF ($p = .032$).

Considering comorbid diagnoses, for participants reporting eye contact discomfort, four were also diagnosed with ASD, four with ADHD, eight with SAD, and two with a psychotic disorder. Of those reporting no difficulties with eye contact, four were diagnosed with ASD, six with ADHD, 14 with SAD and four with a psychotic disorder. Given the small sample size, no statistically

significant diagnostic differences as regards diagnoses were observed based on eye contact sensitivity.

4.3 STUDY III

4.3.1 LONG-TERM INTELLECTUAL, VISUOMOTOR, AND ADAPTIVE FUNCTIONING

4.3.1.1 SELF-REPORTED SOCIODEMOGRAPHIC CHARACTERISTICS

While a majority of participants were single (77%), almost one in four (23%) were in a partnership and many reported having close friends (67%). A minority (20%) lived independently without support. The remainder lived with parents (43%), in their own homes with support (18%), or in residential/sheltered living (19%). Of those with employment (69%), all but one had sheltered or supported employment. Fourteen percent were studying, and 16% had no regular daily occupation. Over half (51%) had attended special schools, and nearly all (92%) had received school support. A substantial majority (76%) needed support to manage their finances.

4.3.1.2 INTELLECTUAL FUNCTIONING INCLUDING STABILITY OF FSIQ AND UNEVEN IQ PROFILE

For the 56 individuals who participated in WAIS testing at T2, mean FSIQ was 68.2 (SD=11.6, range 40-98). No significant difference between sex was observed. FSIQ was stable for the total group and for males, whereas females had a statistically significant decline in FSIQ between T1 and T2 (p=.002). In females a significant decline was also observed in VIQ/Verbal Function (p=.011) Index (VFI), while no significant change was seen in PIQ/Perceptual Function Index (PFI). A strong correlation was found between FSIQ at T1 and FSIQ at T2.

A change of 10 or more IQ points was observed in 18/55 participants (33%) between assessments. Of these, five participants exhibited an increase (range: 10–17 points), while 13 participants exhibited a decrease (range: 10–26 points). Amongst those (n=8) with a large shift, greater than 15 IQ points, two male participants showed an improvement, in one from FSIQ 46 to 62 and the other from FSIQ 57 to 74. The remaining six participants, all female, experienced a decrease.

At follow up, 19 of the 56 participants (34%) exhibited an uneven IQ profile, of whom 15 (27%) exhibited a higher VFI. Regarding stability of "uneven IQ profile"/NVLD, defined as having a higher VFI than PFI (VCI >15 IQ scores PRI), 50 of the 56 participants who were tested with WAIS at T2, had been tested with Wechsler scale tests at T1, allowing for the analysis of "uneven IQ profile"/NVLD. Ten participants had had an "uneven IQ profile" at T1. Five of these maintained this profile at T2, while 9/40 who had an "even IQ profile" at T1 exhibited an "uneven IQ profile" at T2

Eight of the individuals with a psychotic disorder participated in IQ testing at both timepoints. This subgroup demonstrated a significant decline in FSIQ from T1 (*Md* = 73.5) to T2 (*Md*= 68.5, *z* = -1.992, *p* = .046) with a mean decrease of 4.38 (95% CI: 0.31 to 8.45). Also VIQ declined significantly from T1 (*Md* = 86.0) to T2 (*Md* =79.0, *z* = -2.380, *p* = .017), with a mean decrease of 8.75 (95% *CI*: 2.47 to 15.03).

4.3.1.3 LONGITUDINAL OUTCOME IN VISUOMOTOR FUNCTION

There was a significant decline in VMI between timepoints. VMI significantly decreased from T1 (*Md* = 61,5) to T2 (*Md* = 47.0, *z* = -2.943, *p* = .001). In females median VMI scores decreased significantly, from T1 (*Md* = 75) to T2 (*Md* = 58, *z* = -3.141, *n* = 19, *p* = .002), which was not the case for males. At follow-up, o significant difference in VMI between sex was found. A decrease of ≥15 VMI was seen in 12 of the 30 participants (40%) with assessments of VMI at both T1 and T2.

4.3.1.4 LONG-TERM ADAPTIVE FUNCTIONING AND SOCIOECONOMIC VARIABLES

The majority had a need of substantial support in daily life regarding living, education/employment, and economy. The mean GAF-score at T2, 50.5 (*SD* =11,6, range 25-72) indicating moderate to severe psychiatric symptoms and impairment in social, educational/occupational, and psychological functioning. The impact of T1 FSIQ, NDD, EF, age at T2, and sex, on GAF at T2 was investigated using multiple linear regression. Results showed a significant association between FSIQ at T1 and GAF at T2. Nevertheless, the adjusted r2 exhibited that the overall model explained only for 8.2 % of the variability in GAF.

Regarding VMI, Pearsons's correlation analysis presented a moderate positive correlation of VMI at T1 and GAF at T2 (*r*=.377 (*CI* = .094 - .604), *n*=45, *p*=.011).

4.4 STUDY IV

4.4.1 ADULT HEALTH OUTCOMES AND PHENOTYPIC DIVERSITY

4.4.1.1 PHYSICAL CONDITIONS

The group exhibited a high rate of various health conditions. Physical health problems were common, with participants reporting an average of 3.2 medical conditions (ranging from 0 to 6). Only 3% reported no medical problems, while 42% had four or more conditions.

CHD and VPI co-occurred in 32%. CHD, either alone or in combination with other conditions, were present in 62% of participants. Specific types of CHD included tetralogy of Fallot, in 12, atrial or ventricular septal defects in 16, aortic arch anomalies, in 10, pulmonary atresia in 3, patent ductus arteriosus in 3, and truncus arteriosus in 5. No link was found between CHD and NDDs, or specific psychiatric conditions.

VPI was a common finding, affecting 46 (58%) of the participants, at least 27 of whom had undergone surgery. The prevalence of autism was significantly lower in individuals with VPI compared to those without ($\chi 2$ (1, n=79) = 5.25, p = .02, *phi* = -0.29). No significant associations were found between VPI and ADHD or ID.

Thymus: Eight participants (10%) had thymus aplasia, all of whom also had a CHD. The association between thymus aplasia and CHD approached statistical significance ($\chi 2$ (1, n=79) = 3.80, p = .051, *phi* = .26). Notably, a significant association was found between the absence of VPI and thymus aplasia ($\chi 2$ (1, n=79) = 5.70, p = .017, *phi* = -.31). However, thymus aplasia was not significantly associated with susceptibility to infections or autoimmune disorders.

Susceptibility to infections: Childhood infections had been common in this group; however, only three females remained susceptible to infections in adulthood. Two of these reported receiving immunoglobulin replacement therapy (IGRT). While many participants experienced a decrease in susceptibility to infections in adulthood many reported that the episodes, when experiencing infections, were more severe and prolonged.

Autoimmunity: Eighteen participants (23%) reported autoimmune disorder, including inflammatory bowel disease (IBD, *n*=2), psoriatic arthritis (*n*=2), celiac disease (*n*=7), rheumatoid arthritis (*n*=5), idiopathic thrombocytopenic purpura (ITP, *n*=3), autoimmune thyroiditis (*n*=2), and alopecia areata (*n*=1). Some participants had more than one autoimmune disorder.

Thyroid: Twenty-two participants (28%) had hypothyroidism, with at least two cases stemming from prior Graves' disease. A significant association was found between thyroid disorders and overall autoimmune conditions (χ^2 (1, *n* = 79) = 7.21, *p* = .007, *phi* = .34). In contrast, hypoparathyroidism, presented in 20 (25%) of participants was not linked to autoimmunity.

Gastrointestinal problems: Twenty-six participants (33%) reported gastrointestinal problems, including celiac disease, inflammatory bowel disease (IBD), gastroesophageal reflux disorder, and constipation. Abdominal pain and nausea were also reported.

Renal problems: Three participants (4%) had unilateral renal agenesis, and one had hydronephrosis.

Neurological conditions: Eight participants experienced seizures in adulthood, and four others had experienced seizures in childhood, suggesting a relatively high prevalence of epilepsy.

Hearing impairment: Conductive, sensorineural, or mixed impairments, affected 33 participants (42%). No significant association was observed with velopharyngeal insufficiency.

Sleep Problems: Sleep difficulties, particularly initiating or maintaining sleep, were reported by 29 participants (37%), with a higher prevalence among females. Eleven of these participants used sleep medication, melatonin being the most common (*n*=8). Sleep problems were significantly associated with anxiety disorders (χ^2 (1, *n*=79) = 9.37, *p* = .002, *phi* = .37). No such association was found with mood or psychotic disorders, or NDDs.

4.4.1.2 HEALTHCARE CONTACTS

Of the 79 participants, 17% (*n*=13) had no systematic follow-up, 28% (*n*=22) were followed only in a primary care clinic (PCC), and 56% (*n*=44) had follow-up at one or more specialized clinics. Among the 49 participants with CHD, 57%, (*n*=28) were followed at an Adult Congenital Heart Disease (ACHD) clinic, 31% (*n*=15) in their PCC, and 12% (*n*=6) had no cardiac

follow-up. Those without cardiac follow-up were deemed not requiring systematic cardiac follow-up in adulthood. For the 34 participants (43%) with thyroid dysfunction and/or hypoparathyroidism, 59% (*n*=20) were followed in a PCC, and 41% (*n*=14) were followed at an endocrinology unit.

4.4.1.3 PSYCHIATRIC, PSYCHOPHARMACOLOGICAL AND PSYCHOTHERAPEUTIC INTERVENTIONS

A majority of the participants, 58 (73%,) did not utilize psychiatric services, even though eight (10%) of this group expressed a desire for such services. Conversely, 21 (27%) were in regular contact with psychiatric services. Psychotropic medication use was reported by 27 of participants (34%). This included antidepressant use in 20 (25%), including Selective Serotonin Reuptake Inhibitors (SSRIs), Selective Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs), or bupropion), antipsychotic use in nine (11%), including aripiprazole, risperidone, clozapine, olanzapine, or quetiapine), and five (6%) using mood stabilizer including lamotrigine, lithium, or valproate acid. Only 4/36 of participants (11%) with ADHD received ADHD medication – three were prescribed stimulants, and one atomoxetine. Psychotropic medication use was similar between sexes. Finally, 17% (*n*=13) of participants had or were receiving psychotherapeutic mental health support.

4.4.1.4 PREVALENCE OF HYPERPROLINEMIA AND ANY ASSOCIATIONS WITH IQ, NDDS AND PSYCHOTIC SYNDROMES

The average plasma proline level was 372 µmol/L (*SD* 177), ranging from 170 to 1140 µmol/L. Hyperprolinemia (defined as plasma proline levels above 316 µmol/L in females and 377 µmol/L in males) was present in 18/34 participants (53%). However, no statistically significant association was found between severe hyperprolinemia (defined as >500 µmol/L) and NDDs, epilepsy, or psychiatric disorders, including psychosis, at follow-up (T2).

5 DISCUSSION

5.1 GENERAL FINDINGS

This longitudinal prospective, study of physical and mental health, including cognitive, neurodevelopmental, and adaptive functioning in 22q11.2DS from childhood to adulthood highlights the diverse and evolving support needs of these individuals. Varying levels of support were required across domains including primary care, psychiatry, education, employment, and daily living, such as financial management.

5.2 STUDY I

5.2.1 MENTAL HEALTH AND NDDS

In this longitudinal study of 79 adults with 22q11.2DS, a majority exhibited NDDs and/or BIF or mild ID, impacting daily functioning and mental health. The prevalence of mild ID (62%) was much higher than that of the general population (Maulik et al., 2011), yet in line with prior research on individuals with 22q11.2DS (Green et al., 2009). While ID stability was generally strong, a subgroup experienced significant IQ increases, while a larger subgroup experienced significant decreases, highlighting the need for ongoing cognitive monitoring.

NDD diagnoses remained stable, with individuals meeting criteria for childhood NDDs continuing to meet those criteria in adulthood. However, a substantial subgroup met criteria for ADHD, ASD, or both later in life. Increased difficulties in adulthood, and the relatively young age of some participants at initial assessment, may account for this. In contrast to some studies (Schneider et al., 2014), rates of ASD and ADHD were higher in our adult sample compared to childhood/adolescent samples.

Depressive disorder was highly prevalent (43%) in our 22q11.2DS sample, significantly exceeding the 16% lifetime prevalence in the general population (Kessler et al., 2003). Conversely, the higher rate of depression in males in our sample contrasts with the higher prevalence among females in the general population (Salk et al., 2017). Bipolar disorder prevalence was similar to other 22q11.2DS studies (Schneider et al., 2014) and to general population rates (Rowland & Marwaha, 2018).

Anxiety disorders were very common, nearly 50% lifetime prevalence in our sample, with panic disorder and social anxiety disorder being most common. This is higher than the reported 30 % lifetime prevalence for females and 20% for males (McLean et al., 2011). OCD prevalence, nearly 20%, was also elevated compared to the general population (Ruscio et al., 2010), but consistent with other studies in 22q11.2DS (Baker & Skuse, 2005; Gothelf et al., 2004).

Our study found no cases of PTSD in the sample, consistent previous reports of lower PTSD prevalence (0.9%) in 22q11.2DS compared to the general population (3.9%) (Koenen et al., 2017; Schneider et al., 2014). However, a recent Dutch study of 112 adults with 22q11.2DS reported a significantly higher prevalence of PTSD (8.0%), indicating potential underdiagnosis (von Scheibler et al., 2022). The higher prevalence found in the Dutch study may stem from differences in trauma exposure or diagnostic approach.

Eating disorder prevalence in our sample was consistent with that of the reported worldwide prevalence, approximately 1%; (Qian et al., 2022), however both anorexia and bulimia nervosa are more common in the general population in Sweden than reported(Karjalainen et al., 2016; Råstam et al., 1989) No studies of eating disorders in 22q11.2DS were identified. Alcohol and substance use disorders were uncommon in our 22q11.2DS sample, similar to previous research (Schneider et al., 2014; Vingerhoets et al., 2019) and lower than rates observed in the general population (Glantz et al., 2020; Grant et al., 2016).

No participants in our group displayed conduct or antisocial personality disorder, contrasting with higher rates observed in groups where ADHD rates usually are high, e.g. individuals in correctional services (Billstedt et al., 2017). This finding is consistent with a study showing reduced comorbidity between 22q11.2DS and oppositional defiant disorder/conduct disorder, even in those with ADHD (Niarchou et al., 2015).

Our study found a lower prevalence of psychotic symptoms (14%) than previously reported (20%–40%)(Gothelf et al., 2013; Murphy et al., 1999; Schneider et al., 2014), aligning more closely with findings from studies in non-psychiatric settings (Hoeffding et al., 2017). Unlike the general population's male predominance in psychotic disorders (Blokland et al., 2022), our results, consistent with the IBBC study (Schneider et al., 2014) showed no sex difference.

Of the 11 individuals exhibiting a psychotic disorder, three met criteria for schizophrenia spectrum, three for schizoaffective disorder and three had psychotic symptoms linked to mood disorder episodes. Also, two of the participants who experienced psychotic symptoms had transient episodes related to stress. The lower rate compared to prior studies (Fiksinski et al., 2017; Vorstman et al., 2013) may reflect earlier diagnosis and treatment of comorbid NDDs/IDs in our sample which may have led to psychoeducational interventions, supportive care adaptations, and, when warranted, pharmacologic and psychological therapies.

While antipsychotics were prescribed to only one-third of the psychotic group, all with schizoaffective symptoms received mood stabilizers, potentially indicating underdiagnosis and undertreatment. In contrast to findings from other reports (Fiksinski et al., 2017; Vorstman et al., 2013) ASD at T1, in our sample, was more common in participants who developed psychosis, although this difference was not statistically significant. Those with psychotic symptoms also had lower mean GAF scores, underscoring the need for enhanced support and accommodations.

5.3 STUDY II

5.3.1 SELF REPORTED EYE CONTACT SENSITIVITY AND FACE PROCESSING

This study investigated eye gaze discomfort in young adults with 22q11.2DS. Approximately half of participants reported discomfort with eye contact, particularly with strangers, correlating with reduced eye contact, especially toward neutral or ambiguous faces (Mobach et al., 2022; Nudelman et al., 2022; Schurgin et al., 2014; Tottenham et al., 2013) Combining subjective and objective measures provided a more comprehensive understanding of eye contact sensitivity, particularly valuable for neurodivergent populations (Ridley et al., 2022). This supports the use of self-reported assessments in clinical populations with social, intellectual, or communication impairments (Ridley et al., 2022; Shipman et al., 2011).

This study reveals that eye gaze discomfort in 22q11.2DS is associated with atypical face scanning. Specifically, participants experiencing eye gaze discomfort showed a reduced lateralization of face processing, failing to exhibit the typical LVF bias reflecting the brain's right-sided lateralization for

face processing. While previous work documented atypical visual scanning patterns in 22q11.2DS (Campbell et al., 2010; Franchini et al., 2016; McCabe et al., 2011). This study is the first to link atypical lateralization to eye gaze sensitivity.

Similar atypical patterns in LVF bias have been found in other conditions, including dyslexia, social anxiety, autism, and depression (Löwenberg et al., 2020; Masulli et al., 2022). Future studies should investigate the underlying mechanisms, as appropriate attention to faces, particularly early in development, may promote neural specialization and social functioning (Johnson, 2000; Klin, 2008; Schultz, 2005; Vacas et al., 2022). Research suggests that oversensitivity to faces and eye contact in autism may negatively impact social development by interfering with typical social interaction. (Hadjikhani et al., 2018).

5.4 STUDY III

5.4.1 LONG-TERM INTELLECTUAL, VISUOMOTOR AND ADAPTIVE FUNCTIONING

Participants in our group reported major and diverse needs of support across domains, regarding physical and mental health issues, education, employment, and daily living, including private economy. Partnership rates were low (23%), consistent with other studies (Mosheva et al., 2018), while close friendships were common, suggesting strong social connections despite 22q11.2DS challenges. Some participants may have included significant others, such as siblings or caregivers, in their friendship definitions.

Intellectual functioning ranged from borderline to mild intellectual disability, consistent with previous studies (Bassett et al., 2005; Butcher et al., 2012). While some participants showed increases, most experienced a non-significant decrease in FSIQ over time, contrasting with some studies showing significant declines, especially in VIQ (Gothelf, Penniman, et al., 2007; Green et al., 2009; Mosheva et al., 2018), but in agreement with others (Kates et al., 2019)

At follow up, no sex difference in intellectual function was observed. While FSIQ remained stable for the total group and males, females showed a statistically significant decline in FSIQ and VIQ. Importantly, all participants experiencing an IQ decrease exceeding 15 points were female, while the two participants showing an improvement exceeding 15 IQ points were male. This

contrasts with observations suggesting an initial cognitive advantage in girls, which our data shows are not maintained over time, and is consistent with Antshel et al. (Antshel, Conchelos, et al., 2005; Niklasson & Gillberg, 2010). Further research is needed to explore the underlying mechanisms of this age-related decline in females with 22q11.2DS."

Visuomotor skills were significantly impaired at both time points. The mean of 56 on the VMI scale, far below the reference range of 90-109 (Beery, 2010). These difficulties coordinating vision and movement, may have a significant impact on daily living skills. Simple tasks such as tying shoes, eating, and using utensils, which most people perform effortlessly, become challenging and frustrating. Problems with fine and gross motor skills and coordination can negatively affect all sorts of physical activities. Furthermore, visuomotor difficulties can impair reading, writing and social performance.

Uneven cognitive IQ profiles (VIQ > PIQ) were prevalent, but only half of those presenting this profile at T1 continued to do so at follow up. A significantly higher proportion of participants had a VFI exceeding their POI (VCI $\geq$15 IQ scores PRI), potentially mirroring NVLD characteristics (Margolis et al., 2020). This suggests a need for careful assessment to avoid misinterpreting stronger verbal skills as masking underlying difficulties.

In our psychosis subgroup (*n*=8), FSIQ scores significantly declined over time, particularly VIQ, contrasting with stable PIQ. This findings fit with findings from previous research (Gothelf et al., 2013; Schneider et al., 2014; Vorstman et al., 2015), but our study found unexpectedly higher VIQ/VFI at baseline (T1) in the psychosis group compared to those without a history of psychosis at follow-up (T2). This contrasts with previous research suggesting lower childhood IQ as a risk factor for psychosis (Antshel et al., 2017; Gothelf, Feinstein, et al., 2007; Pontillo et al., 2019).

A diathesis-stress model suggests two potential pathways for development of psychosis; higher verbal ability might heighten stress vulnerability through unmet expectations and insufficient support, or it might enhance stress awareness and thus psychotic symptom vulnerability. Our limited sample size warrants cautious interpretation, despite statistically significant differences in VIQ in the psychosis group at baseline. Crucially, these differences were not present at follow-up, and PIQ and FSIQ did not differ between groups at either time point. These findings suggest that the FSIQ and VIQ decline might be a consequence of or a predictor of psychosis risk.

Baseline intellectual ability significantly predicted later functioning in line with the findings obtained in the study by Butcher (Butcher et al., 2012), but in contrast to those reported in some previous studies (Vangkilde et al., 2016; Wagner et al., 2017). This study's assessment of functioning, primarily using the GAF scale, may limit the scope. Future investigations should use adaptive functioning scales for a more comprehensive understanding.

5.5 STUDY IV

We found a broad diversity of physical disorders in the 79 adults with 22q11.2DS. A majority had CHDs at a prevalence rate similar to those reported in other studies on 22q11.2DS (Goldmuntz et al., 2024). In line with other studies on children e.g. Yi et al. (Yi et al., 2014), we found no links between CHD and NDD or psychiatric disorders in adulthood. However, Yi's group in Pennsylvania found that rates of neurocognitive impairments were significantly more common in children with 22q11.2DS and CHD compared to those with CHD with no 22q11.2DS. This may indicate an increased susceptibility to NDDs and psychiatric conditions in cases with CHD in 22q11.2DS.

More than half in our group had mild to severe velopharyngeal insufficiency. A prior study (Persson et al., 2012) found that a significant proportion of adults with 22q11.2DS continue to experience moderate to severe velopharyngeal impairment, even after surgery, consistent with earlier findings in children (Solot et al., 2001). Audible nasal airflow and hypernasality were the most prevalent symptoms.

Our participants reported a very significant decrease (from 52% to 4%), as regards susceptibility to infection in adulthood. Two participants (3%) received IGRT, consistent with findings of a study of 855 individuals with 22q11.2DS, where 3% received IGRT (Patel et al., 2012). Patients with 22q11.2DS displays variable immunodeficiency and autoimmune phenotypes, even among individuals with identical deletions (McLean-Tooke et al., 2007). Abnormal development of the pharyngeal arches in 22q11.2DS results in defects of the parathyroid glands, thymus, and conotruncal heart region. Complete DiGeorge syndrome, characterized by complete thymus absence and severe T-cell deficiency, is, however, rare (occurring in only ~0.5% of cases). Partial thymus defects are common, leading to impaired immune function, often involving both T-cell and B-cell deficiencies, and increasing the risk of autoimmune disorders (Mustillo et al., 2023; Patel et al., 2012). A significant

proportion (up to 30%) develops autoimmune diseases (Crowley et al., 2022). Factors such as increased infection rates, aberrant T-regulatory cell development, and reduced thymic tolerance contribute to the development of autoimmunity in this condition. but the relationship between immune defect severity and autoimmune risk remains unclear (McLean-Tooke et al., 2007).

A Norwegian nationwide study (Lima et al., 2011) of 59 individuals with 22q11.2DS found a high prevalence of hypoparathyroidism (47%) and a correlation between hypoparathyroidism and autoimmune disorders (10% of participants, all female). In contrast, our study of adults with 22q11.2DS found a lower rate of hypoparathyroidism (25%) and no correlation between hypoparathyroidism and autoimmunity. We did, however, find a moderate association between thyroid disorders and several other autoimmune disorders, including rheumatoid arthritis, inflammatory bowel disease (IBD), celiac disease, Immune Thrombocytopenic Purpura, psoriasis, alopecia areata, Hashimoto's thyroiditis, and Graves' disease.

One in ten of our participants had epilepsy. Four participants had had epilepsy during childhood but no longer experienced it in adulthood. A review (Bayat & Bayat, 2022) highlighted a high prevalence of epilepsy, movement disorders, neuropsychiatric disorders, and atypical neuroimaging in 22q11.2DS. That review also noted increased risks for Parkinson's disease and dystonia. Our study did not assess these specific diagnoses or nor did we carry out neuroimaging. In the review by Bayat and Bayat polymicrogyria was a notable neuroimaging finding, suggesting neurological presentations may be early indicators in 22q11.2DS. Improved awareness of the condition's broad neurological spectrum is crucial for better patient care.

Hearing impairment was prevalent in our 22q11.2DS group, nearly half, consistent with prior research (Persson et al., 2012). A review (Verheij et al., 2017) found a wide range (6.0%–60.3%) of hearing loss in 22q11.2DS, predominantly mild conductive hearing loss, with sensorineural and mixed types also reported. A Dutch study (von Scheibler et al., 2024) also found hearing loss common in adults with 22q11.2DS, often starting young. Severity was associated with older age and a history of chronic otitis media. The authors of the review and of the Dutch study recommended regular audiometric screening starting in early adulthood.

Gastrointestinal (GI) problems, primarily constipation, affected one-third of participants. Autoimmune GI conditions, like IBD and celiac disease, were

significantly more common than expected (Ng et al., 2017; Singh et al., 2018). A study (Kotcher et al., 2022) found a high lifetime prevalence (91%) of GI problems in adults with 22q11.2DS, generally improving with age. Common functional GI problems included constipation, gastroesophageal reflux disorder (GERD), and functional abdominal pain. Structural or autoimmune GI complications were not markedly elevated.

We found lower rates of urogenital problems than previously reported. A review (Van Batavia et al., 2019) of 1,073 children with 22q11.2DS revealed structural kidney/urinary tract anomalies in 15%, with genital anomalies more common in boys and generally mild. Our lower rates may be the result of less extensive screening. Van Batavia et al. recommended renal/bladder ultrasounds alongside routine examinations in 22q11.2DS.

Our findings show that, in line with previous studies, approximately 50% of individuals with 22q11.2DS have elevated proline levels (da Silva Alves et al., 2011; Squarcione et al., 2013). High levels of proline may disrupt the brain's glutamatergic system, vital for cognition and memory (Raux et al., 2007). Disruptions in glutamatergic signaling are associated with cognitive impairments and psychosis in 22q11.2DS (Jacquet et al., 2005; Raux et al., 2007; Vorstman et al., 2009).

However, studies on 22q11.2DS and elevated proline levels have yielded conflicting results. While Jacquet et al. linked moderate hyperprolinemia to certain forms of psychosis, Raux et al. found no correlation between proline levels and psychiatric disorder in a larger group (n=92). However, in a subgroup with extremely high proline levels (n=7, >550 μmol/L), Raux et al. observed an inverse correlation between proline and IQ, as well as an association with psychotic symptoms. Although some studies suggest a possible link between hyperprolinemia and mental disorders such as schizophrenia, a systematic review (Namavar et al., 2021) concluded that existing evidence doesn't definitively support this link, emphasizing the potential roles of both genes and the environment.

5.6 STRENGTHS AND LIMITATIONS

5.6.1 STUDY I

This prospective, longitudinal study examined a large cohort of individuals with 22q11.2DS, assessing mental health and comorbidities across many years.

While the sample size, though relatively large for this specific condition, may have been insufficient to detect statistically significant differences in some analyses, requiring non-parametric tests, the study highlights the need for replication in larger, independent samples. Although 21 participant dropouts (21%), baseline key characteristics were similar between those who completed the study and those who did not, indicating that attrition did not introduce substantial bias to the results. Despite these limitations this study shows a high risk of NDDs, psychiatric problems, cognitive impairment and reduced overall functioning over time.

5.6.2 STUDY II

While innovative, the study has its limitations. The small sample size, while comparable to those of similar studies (Campbell et al., 2010; Leleu et al., 2016; McCabe et al., 2011), makes it necessary to be cautious when drawing conclusions. Future research should attempt to replicate these findings in larger samples and utilize more comprehensive methodologies, including multidimensional analyses of eye gaze discomfort (e.g., detailed interviews, physiological measures, video analysis, proxy reports), and assessments of broader lateralization (e.g., language and hand dominance). Despite these limitations, the study's results suggest that self-reported eye gaze discomfort can reveal subgroups with distinct face processing alterations and greater daily challenges in individuals with 22q11.2DS.

5.6.3 STUDY III

This relatively large, longitudinal study of intellectual, adaptive, and functional development in 22q11.2DS, spanning nearly two decades, offers valuable insights into lifespan trajectories. However, limitations exist. Longitudinal designs require substantial follow-up periods, and attrition reduced the sample size, hindering the identification of significant differences and specific predictors of functioning. The absence of an IQ-matched comparison group was also a limitation, inherent in the longitudinal design. While well-validated tests were used, the change from WISC to WAIS between timepoints might show a change in IQ scores due to different normative comparison groups across the two tests. Present data indicate that use of WAIS tend to result in somewhat higher scores, so the change from WISC to WAIS could be assumed to have “minimized” the global IQ decline seen on the whole, rather than overstating it (Kaufman, 2006). Despite some attrition, the study's follow-up group remained representative, as there were no significant differences in FSIQ, gender, or age at the follow-up timepoint (T2) between participants and

non-participants from T1 to T2. In spite of these limitations, the results presenting that overall group intelligence remained steady, individual declines were observed suggesting the need for clinical long-term follow-up, to provide personalized support and address the significant risk of psychosis, especially if VIQ declines, potentially indicating or resulting from psychosis in this group.

5.6.4 STUDY IV

Strengths of the study include the relatively large study group that had been followed from childhood and that the adult group with 22q11.2DS could be clinically assessed and evaluated through their medical records. Limitations were mainly due to lack of collection of systematic medical data, such as from neuroimaging and from specific immunological analyses with regard to autoimmunity. Despite its limitations the findings highlight the complex clinical challenges faced by individuals with 22q11.2DS, necessitating multidisciplinary care and follow-up.

6 CONCLUSIONS AND CLINICAL IMPLICATIONS

6.1.1 STUDY I

22q11.2DS is strongly associated with high rates of psychiatric disorders often co-occurring with neurodevelopmental conditions. Stable NDD diagnoses across the lifespan are observed, with childhood ASD linked to an increased risk of adult psychosis, though the overall rate in our sample was lower than previously reported. Clinicians should be aware of the potential for 22q11.2DS in adults presenting with anxiety, mood, psychotic, or neurodevelopmental symptoms, particularly those with borderline intellectual functioning or intellectual disability.

6.1.2 STUDY II

Conclusion: Our results show that, by asking individuals with social communication disorders about eye gaze discomfort can help us better understand their specific challenges. Combining these self-reports with eye-tracking data provides insights into their face processing abilities and the extent of impairment in this population of individuals with 22q11.2DS.

6.1.3 STUDY III

Individuals with 22q11.2DS, while showing stable average intellectual functioning, experience substantial individual declines. An “uneven IQ profile” with a disproportionately stronger VIQ risk mask lower overall intellectual abilities (FSIQ), potentially leading to underestimation of cognitive difficulties and consequent inadequate support or excessive demands."

Declines in FSIQ and VIQ may signal a predisposition toward, or be a consequence of, a psychotic disorder. Longitudinal monitoring of functioning in individuals with 22q11.2DS is critical. Given the high prevalence of intellectual impairment, routine clinical assessments, including neuropsychological testing when appropriate, are essential to thoroughly evaluate cognitive abilities, adaptive skills, executive functions, and identify psychiatric and neurodevelopmental disorders. This approach allows for personalized interventions and support, adapting as needed over time, to foster optimal health and development in this vulnerable population.

6.1.4 STUDY IV

This study reveals the complex clinical presentation of 22q11.2DS, highlighting the diverse medical and psychiatric challenges faced by affected individuals. The variability in these problems, both between individuals and across a person's lifespan, is significant.

7 FUTURE PERSPECTIVES

Future research is needed to track the long-term development of NDDs and psychiatric conditions in larger groups of adults with 22q11.2DS. Currently, there's limited knowledge about effective interventions and treatments for these conditions in adults with 22q11.2DS, particularly considering the co-occurrence of medical and psychiatric issues. Research should also examine how adaptive functioning and quality of life are affected. A combination of qualitative and quantitative approaches would greatly benefit understanding these complex issues.

Research is needed to establish causality and explore developmental mechanisms underlying the observed associations between eye gaze discomfort and weakened lateralized face processing in 22q11.2DS.

Longitudinal studies on larger samples of adults with 22q11.2DS are needed to examine cognitive development over time, including visuomotor performance. Previous research linked low childhood FSIQ to psychosis risk, while our findings suggest higher baseline FSIQ and VIQ, with declines specifically in those who developed psychosis. These differing results warrant further investigation in larger, independent studies to explore potential explanations, such as differences in study populations, assessments, or the stage of psychotic disorder.

More research is needed to understand the complex immune system issues including autoimmunity in 22q11.2DS. The field of immune psychiatry offers significant potential for understanding the interplay between immune dysfunction and the mental health challenges faced by individuals with 22q11.2DS.

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