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Neurodevelopmental and other psychiatric disorders in 22q11.2 deletion syndrome from childhood to adult age: Prospective longitudinal study of 100 individuals

Lena Wallin [1,2] | Christopher Gillberg [1,3] | Elisabeth Fernell [1,3] | Carina Gillberg [1,3] | Eva Billstedt [1,3]

[1]Gillberg Neuropsychiatry Centre, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

[2]Department of Psychiatry, Cognition and Old Age Psychiatry, Sahlgrenska University Hospital, Gothenburg, Sweden

[3]Child Neuropsychiatry Clinic, Sahlgrenska University Hospital, Gothenburg, Sweden

Correspondence
Lena Wallin, Gillberg Neuropsychiatry Centre, Institute of Neuroscience and Physiology, Sahlgrenska, Academy, University of Gothenburg, Gothenburg, Sweden.
Email: lena.b.wallin@vgregion.se

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Abstract

The 22q11.2 deletion syndrome (22q11.2DS), affects physical as well as cognitive and emotional functioning with increased risk for psychiatric and behavioral problems. This longitudinal study of 79 individuals (18–50 years) with 22q11.2DS investigated neurodevelopmental (NDD) and psychiatric disorders in adulthood, evaluated the stability of childhood diagnoses over time, and examined associations between clinical characteristics in childhood/adolescence and diagnostic outcome in adult age. Examination using validated instruments for cognitive, psychiatric, and global functional problems in the context of an in-depth clinical evaluation found adult age stability of NDD diagnoses made in childhood, however, rates increased at follow-up. Rates of anxiety, mood, and psychotic disorders were high, with a majority meeting diagnostic criteria for one or more psychiatric disorder. The rate of psychotic disorders was much lower compared to many other studies. Variability in functioning at follow-up was primarily associated with intellectual ability at T1. The findings obtained highlight the increased risk of NDD and psychiatric problems and of cognitive impairment and reduced levels of global functioning over time. Results emphasize the importance of clinical follow-up to enable appropriate support for the promotion of optimal health along with a need for future research on effective interventions and treatment strategies.

KEYWORDS
22q11.2 deletion syndrome, follow up, neurodevelopmental, psychiatric, phenotype, behavior

1 | INTRODUCTION

The 22q11 deletion syndrome (22q11.2DS), previously often referred to as DiGeorges syndrome, velocardiofacial syndrome or cardiac defects, abnormal facial features, thymic hypoplasia, cleft palate, and hypocalcemia (CATCH 22), is a syndrome that involves genetic microdeletions resulting in a heterogeneous clinical presentation. Duplications at the same locus, 22q11 duplication syndrome (22q11DupS), have been less described but the very few studies published on this syndrome report a range of symptoms of various severities and affecting many organ systems (Bartik et al., 2022; Bhattarai et al., 2023; Hoeffding et al., 2017). A multicentre study reported a

frequency of 22q11.2DS in 1 per 992 in low-risk pregnancies (Grati et al., 2015). Other studies report a prevalence of 1 in 2000–6000 in newborns (Botto et al., 2003; Oskarsdottir et al., 2004; Shprintzen, 2008). Based on a prevalence of approximately 25 per 100,000 births, the Swedish National Board of Health and Welfare estimates a rate of about 30 affected infants born annually in Sweden and in 2019 fewer than 400 individuals had been diagnosed with the syndrome in Sweden (The National Board of Health and Welfare, 2019). In Sweden, with good testing availabilities, the reason for unidentified 22q11.2DS might be that the condition is not suspected due to limited knowledge about the syndrome and that the symptoms in childhood vary and can be mild, not causing need for referrals to health care.

The syndrome can cause malformations and dysfunctions in a wide range of organ systems of varying degrees, from very mild to severe (McDonald-McGinn et al., 2015). Neurobehavioral manifestations of the condition can include cognitive impairments, behavioral problems, and a high rate of psychiatric disorders such as anxiety syndromes, mood disorders, and schizophrenia/other psychotic syndromes. Increased rates of neurodevelopmental disorders (NDDs), for example, autism spectrum disorders (ASD), attention-deficit/hyperactivity disorder (ADHD), and intellectual disability (ID) have also been reported (Niklasson et al., 2001, 2009; Swillen et al., 2018; Swillen & McDonald-McGinn, 2015). In a large international multicenter study of 1402 individuals with 22q11.2DS aged 6–68 years (Schneider et al., 2014), ADHD (especially the inattentive type) was the most common (37%) disorder in childhood. ASD was most common in the adolescent group (27%) with a similar frequency as ADHD (24%). Anxiety disorders were common at all ages (31%). Likewise, obsessive-compulsive disorder (OCD) was more common with an odds ratio of 2.1 in 25 adolescents and young adults with 22q11.2DS compared to 25 IQ- and age-matched controls (Baker & Skuse, 2005), and in a study by Gothelf on 43 deleted individuals 33% fulfilled DSM-IV criteria for OCD (Gothelf et al., 2004). The prevalence of mood disorders increased with age to 20% in adulthood, however, the rate of bipolar disorder did not seem to be increased compared to the general population. The prevalence of substance use and conduct disorders (CDs) were low in this population (Schneider et al., 2014), findings also reported in another multicenter study of 434 individuals (Vingerhoets et al., 2019). Finally, psychotic disorders had a higher frequency at all ages and increased from 10% in adolescence to 41% in young adulthood (Schneider et al., 2014).

The increased frequency of psychotic disorders has been reported in studies since the 1990s. Green et al. (2009) reported a 25-fold increased risk of developing psychotic disorders in individuals with 22q11.2DS compared to a 0.7% lifetime risk in the general population (McGrath et al., 2008). In a multisite study (Weisman et al., 2017) of 692 individuals without manifestations or history of psychosis, with the deletion, ages 6–55 years, assessed with Structured Interview for Prodromal Symptoms, more than half (54%) met criteria for either positive or negative/disorganized subthreshold psychotic symptoms of moderate to high severity. A Danish population-based register study (Hoeffding et al., 2017), showed a lower risk for schizophrenia and related psychotic disorders albeit with a seven-fold relative risk in 302 individuals with the deletion or duplication. A longitudinal study of a group originally assessed at around 12 years of age and then reassessed about 5 years later reported a marked increase in psychotic disorders even at late adolescent ages (Gothelf et al., 2007). Although this high rate of reported psychotic disorders in 22q11.2DS it has been questioned if subthreshold psychotic symptoms predict later psychotic disorder, since most individuals with these symptoms did not progress into psychosis, instead a majority many at ultra-high risk for psychosis developed other psychiatric disorders such as anxiety or mood disorders (Lin et al., 2015).

Since socio-communicative deficits are present in both ASD and psychotic disorders it has been hypothesized that typical ASD traits might be prodromal symptoms of psychotic disorders (Ghaziuddin & Ghaziuddin, 2020; Kincaid et al., 2017). In a follow-up study of 120 adolescents, diagnosed with autism in childhood, several psychiatric and other medical disorders were diagnosed at ages between 17 and 40 years. Catatonia was found to be quite common (12%) and psychosis had been diagnosed by an adult psychiatrist in 8% (Billstedt et al., 2005). In a retrospective study about half of 46 young adults diagnosed with schizophrenia had major indications of ASD in childhood (Unenge Hallerbäck et al., 2012). However, the 22q11.2DS studies of Fiksinski and Vorstman found no relation between autistic symptoms during childhood and development of psychotic disorder in adulthood (Fiksinski et al., 2017; Vorstman et al., 2013).

Possible associations between ADHD and psychotic disorders have also been studied. ADHD inattentive symptoms were higher in individuals with 22q11.2DS with subthreshold psychotic symptoms compared to individuals without 22q11.2DS with subthreshold psychotic symptoms and compared to individuals with a family history of psychosis (Niarchou et al., 2018). In a later longitudinal study of 250 children with 22q11.2DS, mean age of 11.2 years at first assessment and 14.3 years at follow-up, Niarchou et al. (2019) found a strong association between ADHD diagnosis in childhood and development of psychotic symptoms, but only a weak association with psychotic disorder, in adolescence. Presence of inattentive symptoms at any time, rather than change in inattentive symptoms, predicted development of psychotic symptoms (Niarchou et al., 2019).

In a longitudinal study of 411 patients with 22q11.2DS, low initial full-scale IQ (FSIQ) and early cognitive decline were predictors of ensuing psychotic illness (Vorstman et al., 2015). In a review of longitudinal and cross-sectional studies of 22q11.2DS (Tang & Gur, 2018), onset of psychotic disorders was found to occur with a peak in late adolescence, comparable to non-deleted individuals. Predictors of psychosis spectrum outcomes were the same in 22q11.2DS as in the idiopathic clinical risk groups; lower baseline functioning with a subsequent decline in a measure of global cognition/FSIQ and higher baseline psychotic, especially negative, symptoms. Furthermore, dysphoric mood and anxiety were predictors of psychosis in individuals with 22q11.2DS.

Even though the rate of psychopathology is increased in individuals with intellectual dysfunction research suggested a further increased risk for psychopathology, independent of IQ, in 22q11.2DS. Assessments showed higher rates of anxiety, ADHD, ASD, and mood

disorders in 22Q11.2DS compared to idiopathic ID as well as compared to IQ-matched controls, and no association was found between increased rate of psychopathology and IQ in 22q11.2DS (Baker & Skuse, 2005; Fiksinski et al., 2018).

Despite many studies focusing on specific psychiatric or NDD syndromes in 22q11.2DS, studies evaluating the whole range of NDDs and psychiatric disorders that the individual might suffer from, and how these develop over time, are few. Also, studies on psychiatric comorbidity are limited, but existing literature (Niarchou et al., 2014; Schneider et al., 2014) reported high frequencies especially between anxiety, mood, and psychotic disorders and between ADHD and anxiety disorders. Multimorbidity in 22q11.2DS was significantly more prevalent in ages 25–44 years compared to the general population at the same ages as well as compared with the older age group 45–64 years (Malecki et al., 2020). Predictors of multimorbidity were older age and psychotic illness, but not sex, major congenital heart disease, or ID.

Here, we report on the prospective longitudinal study of 100 individuals who were included in our original study of a representative cohort with 22q11.2DS at a mean age of 11.4 years (*SD*=7.2, age range 1–35 years, 87 of whom were under age 18 years). In the original study (T1) we found a large proportion of NDDs, including ID. ADHD was much more common than ASD. Forty-four percent of the study group at T1 had ASD and/or ADHD, and 51% had ID. One-third of the study group had neither ID, ADHD nor ASD at T1.

The major aims of the follow-up study were to estimate and rate the types of (i) current psychiatric, (including schizophrenia and other psychotic syndromes) and NDD diagnoses, (ii) stability of NDD diagnoses from childhood to adult age, (iii) to what extent NDD at T1 predict psychosis at T2.

2 | METHODS

2.1 | Procedure and participants

Original assessments at T1 had been performed at the Child Neuropsychiatry Clinic (CNC) in Gothenburg during the period 1997–2005 (Niklasson et al., 2001, 2002, 2005, 2009; 2010) and included 100 individuals (58 females and 42 males, ages 1–35 years, *n*=87 <18 years) with 22q11.2DS, confirmed by FISH analysis. The original group consisted of the 100 first consecutive cases with 22q11.2DS who were referred from the Region Västra Götaland for neuropsychiatric evaluation at the CNC. The study protocol at T1 included diagnostic evaluation according to DSM-IV regarding ADHD, ASD, ID, Tourette syndrome, OCD, and CD performed by a Child and adolescent psychiatrist or a Child neurologist. Semi-structured and structured interviews were used to collect clinical data. The original study also included a comprehensive neuropsychological assessment.

2.2 | Follow-up study group

All individuals included at T1 were at least 18 years of age at follow-up in 2016–2021, and all were thus targeted for participation. The mean follow-up period was 17.0 years (*SD* = 2.4; range: 12–23). The period for data collection was expanded due to the covid pandemic. The study group was initially contacted by letter and then approached by phone. When contact was established, an invitation for a parent to participate in the assessment was posed by the first author. The participant decided if they wanted parental participation. Six individuals were not available for this follow-up study (T2) of whom three had moved abroad and three had died. Nine of the original study group declined to participate and six did not reply to letters, phone calls, or text messages, leaving 79 (34 males and 45 females) for T2 follow-up.

The data collection was performed for the majority of the study group at the research center (*n* = 52), but home visits for those who preferred that (*n* = 12) and digital assessment due to the covid pandemic (*n* = 9), were also carried out. Six participants declined to participate in an individual clinical assessment but agreed for a parent to be interviewed digitally (*n* = 5) or by visit at the centre (*n* = 1).

Informed consent had been obtained at T1 from parents or participants depending on age and ability to consent/assent. At T2, informed consent was obtained from all participants. 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).

2.3 | Measures and assessment methods at T1

Parents completed the Autism Spectrum Screening Questionnaire (Ehlers et al., 1999; Ehlers & Gillberg, 1993; Posserud et al., 2006), the Conners Brief Parent Rating Scale (Conners et al., 1998), the Child Behavior Checklist (Achenbach, 1991) and the Five To Fifteen questionnaire (Kadesjö et al., 2004). Comprehensive DSM-IV diagnoses of ASD and AD/HD were made by the experienced clinical psychiatrist or neurologist taking all available information into consideration.

In addition, cognitive assessment of developmental/intellectual level, visuomotor development, executive functions, and mentalization skills/theory of mind had also been performed by a clinical psychologist (Niklasson et al., 2001, 2002, 2005, 2009).

2.4 | Measures and assessment methods at T2

Evaluation of the clinical/psychiatric status of each participant was performed by a child and adolescent psychiatrist in collaboration with a clinical neuropsychologist. Diagnoses were established based on all available data including the instruments listed below and the clinical appraisal of each participant.

2.4.1 | Clinical assessment

The following schedules/instruments were used:

1. *Structured Clinical Interview for DSM-5 Axis I Disorders*, M.I.N.I. (Sheehan et al., 1998), which is a structured diagnostic

interview for the main psychiatric disorders in the DSM-5 and ICD-10. Validation and reliability studies were conducted comparing M.I.N.I. with SCID-P for DSM-III-R (Spitzer et al., 1992) and with CIDI (a structured interview developed by the World Health Organization). The results of these studies showed that M.I.N.I. had comparable reliability and validity but could be administered in a much shorter time than the aforementioned instruments (Sheehan et al., 1998),

2. The *P.A.R.I.S schedule*, developed by our research group, including a DSM-IV-TR diagnostic schedule to check for autistic symptoms, activity level symptoms, expressive speech development, and medical disorders,
3. The *Global Assessment of Functioning* (GAF) (APA, 1994), rates the general adaptive function in each participant based on all available information. The GAF scale scores range from 0 to 100, and scores below 70 indicate reduced function and need of care/support,

2.4.2 | Cognitive testing

The *Wechsler Adult Intelligence Scales* (WAIS-IV, Wechsler, 2008), a Seven-Subtest Short Form of WAIS-IV (Bulzacka et al., 2016), was used to measure intelligence (Wechsler, 2008). Fifty-five participants participated in IQ testing at both T1 and T2. One more individual participated only at T2. Of the remaining three who did not take the WAIS test at T2 research diagnosis of ID was based upon the results from the test at T1 ($n = 22$) or clinical evaluation ($n = 2$). The vast majority of the T2 IQ tests were performed by the clinical neuropsychologist, but for a subgroup, IQ tests were administered by the child and adolescent psychiatrist under the supervision of the clinical psychologist.

The following questionnaires were used:

1. The *Adult ADHD Self-Report Scale* (ASRS), (Kessler et al., 2005), was completed by both the participant and the parent ($n = 45$), the participant only ($n = 5$), and parents only ($n = 11$). The ASRS scale is a 24-item questionnaire with good psychometric properties including high specificity and high positive predictive value for ADHD (Ustun et al., 2017),
2. The *Fear Survey Schedule-III* (Wolpe & Lang, 1964), was completed by the participants ($n = 51$). The instrument covers five factors representing social, agoraphobic, fears of bodily injury/death, of sexual/aggressive scenes, and harmless animals. Respondents are asked to make intensity ratings on a five-point scale of the degree of their fear in the presence of 76 different situations/objects. Response options range from "not at all disturbed" to "very much disturbed." The instrument's reliability and validity for anxiety disorders have been demonstrated in a variety of contexts (Blankstein et al., 1993).

The parent questionnaire *Adult Behavior Checklist* (ABCL, Achenbach, 1991), and the self-rated *Temperament and Character Inventory* were also included in the study, as well as assessment of emotional processing, using eye-tracking device. We also collected blood samples for genetic and amino acid studies. Results of these measures will be presented in forthcoming studies.

2.4.3 | Statistical methods

Statistical analyses were performed using IBM SPSS Statistics version 28. Independent Sample T-tests in analysis of total group results and nonparametric statistics were used in subgroup comparisons (Mann-Whitney U Test) and in analysis of dichotomous variables (Fishers exact test). All significance tests were two-tailed, and significance level was set at $p<0.05$.

3 | RESULTS

3.1 | Mortality

Three of the 100 individuals of the original cohort had died at the time of the follow-up. The cause of death was reported to be "physical" disorders (tumor and neurodegenerative disorder) in two individuals and a major psychiatric illness (suicide) in one.

3.2 | Psychiatric disorders at T2

Thirty-four (43%) of the total study group (regardless of coexisting NDD or ID) had or had earlier suffered from Major Depressive Disorder (MDD). A somewhat larger proportion of the men, 48%, versus 39% of the women had MDD. Six participants, more males, reported earlier suicidal ideation. Three individuals, one man and two women, met diagnostic criteria for bipolar disorder, though only one of them, a woman, met criteria for mania, the other two had hypomania.

Symptoms of anxiety were frequent, and many participants met criteria, past or current, for one or more anxiety disorders. Panic disorder (PD) ($n = 18$) and social anxiety disorder (SAD) ($n = 16$) were the most frequent. Ten individuals had or had had Agoraphobic Disorder. Nine had or had earlier fulfilled criteria for generalized anxiety dsorder (GAD). More females had SAD and GAD compared to men. OCD was also overrepresented in this group with 14 (18%) individuals, equally divided between gender.

No participant had symptoms of PTSD. One woman had earlier had a diagnosis of eating disorder. One woman and one man used alcohol at a mild level of substance use, however, the vast majority never used alcohol and no other substance use disorders were found. No individual had antisocial personality disorder in the study group (Table 1). There was no significant difference in psychiatric diagnoses with equal gender distribution.

3.2.1 | Psychotic symptoms

Psychotic symptoms of any kind were found in 11 (14%) of our participants, 4 males, and 7 females, but only six (8%) met criteria for Schizophrenia spectrum ($n = 3$) or psychotic disorder ($n = 3$). Two of the three with Schizophrenia were women, one of whom also suffered

TABLE 1 Psychiatric and neurodevelopmental diagnosis ever at follow-up in 79 participants with 22q11.2DS.

Variable	Total $N = 79$ *n* (%)	Males $n = 34$ *n* (%)	Females $n = 45$ *n* (%)
Age, Mean (*SD*)	28.0 (6.6)	28.8 (6.1)	27.4 (7.0)
GAF, Mean (*SD*)	49.3 (11.7)	51 (10)	48 (13)
FSIQ, Mean (*SD*)	68.2 (11.6)	67.0 (8.2)	68.8 (13.1)
Neurodevelopmental disorders			
Intellectual disability	51 (64)	20 (59)	31 (69)
ASD total	28 (35)	11 (32)	17(38)
ASD + ADHD	14 (18)	8 (24)	6 (13)
ASD only	14 (18)	3 (9)	11 (24)
ADHD total	36 (46)	20 (59)	16 (36)
Combined	10 (13)	7 (21)	3 (7)
Inattentive	20 (25)	9 (27)	11 (24)
Hyper/impulsivity	6 (8)	4 (12)	2 (4)
Mood disorders	37 (47)	17 (50)	20 (44)
Depressive disorder	34 (43)	16 (48)	18 (39)
Bipolar disorder	3 (4)	1 (3)	2 (4)
Suicidal ideations	6 (8)	4 (12)	2 (4)
Anxiety syndromes, OCD	37 (47)	15 (44)	22 (50)
Social anxiety	16 (20)	5 (15)	11 (24)
Panic disorder	18 (23)	8 (24)	10 (22)
Agoraphobia	10 (13)	4 (12)	6 (13)
Generalized anxiety	9 (11)	2 (6)	7 (15)
OCD	14 (18)	7 (21)	7 (15)
Psychotic disorders	11 (14)	4 (12)	7 (16)
Psychotic disorder	2 (3)	1 (3)	1 (2)
Psychotic disorder with catatonia	1 (1)	0 (0)	1 (2)
Schizoaffective disorder	3(4)	2(6)	1(2)
Affective Episode with psychotic symptoms	3 (4)	2 (6)	1 (2)

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit/hyperactivity disorder; ASD, autism spectrum disorder; FSIQ, full scale intelligence quote; GAF, global assessment of functioning; OCD, obsessive compulsive disorder.

from catatonia. Three of the six individuals with psychotic disorder had schizoaffective disorder, two men and one woman.

Another three had affective episodes with psychotic symptoms, of whom two men had earlier suffered from recurrent depressive episodes with psychotic symptoms and one woman had psychotic symptoms during manic or depressive relapses. Two women had experienced transient psychotic symptoms with delusions and auditory and visual hallucinations during stresses associated with surgery.

Those with affective episodes with psychotic symptoms had been prescribed mood stabilizers (lithium, atypical neuroleptics, and/or antiepileptics). Of those with schizophrenia only one was currently on antipsychotics due to lack of effect and due to adverse effects for the remaining two.

There was no significant difference in gender or age between the group with and without psychotic symptoms. The mean GAF score for the group with psychotic symptoms at T2 was 44.0 ($SD = 16.7$) compared to 50.2 ($SD = 10.8$) in the non-psychotic group (t (77) $= 1.537$, $p = 0.298$).

3.2.2 | NDD at T1 in the psychotic symptom's subgroup

ASD at T1 was significantly more common in the group with psychotic symptoms compared to those without psychotic symptoms at T2, 6 (55%) of those 11 with psychotic symptoms at T2 had ASD at T1 (X^2 (1, $n = 79$, $= 6.506$, $p = 0.019$). No difference was found between the psychotic and the non- psychotic subgroup in regard of ADHD at T1 (27% vs. 36%).

3.3 | NDDs at T2

Fifty of the 79 (63%) had ASD and/or ADHD at follow-up, 14 of whom had ASD, 22 had ADHD, and 14 had both ASD and ADHD. Thus, 28 of the 79 individuals (35%) met clinical diagnostic criteria for ASD. The proportion with ADHD was significantly higher in males, ($n = 20/34$, 59%) females ($n = 16/45$, 36%), (χ^2 (1) $= 4.227$,

TABLE 2 Stability in neurodevelopmental disorders between original study and follow-up study ($n = 79$).

	Neurodevelopmental disorders at T2				
	No NDD	ASD	ADHD	ASD + ADHD	Total
Neurodevelopmental disorders at T1	$n = 29$ (%)	$n = 14$(%)	$n = 22$ (%)	$n = 14$ (%)	$N = 79$ (%)
No NDD, $n = 45$	27 (60)	5 (11)	7 (16)	6 (13)	45 (100)
ASD, $n = 12$	1 (8)	9 (75)	1 (8)	1 (8)	12 (99)
ADHD, $n = 15$	1 (7)	0 (0)	14 (93)	0 (0)	15 (100)
ASD + ADHD, $n = 7$	0 (0)	0 (0)	0 (0)	7 (100)	7 (100)
Total $N = 79$ (%)	29 (37)	14 (18)	22 (28)	14 (18)	79 (100)

Abbreviations: ADHD, Attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; NDD, neurodevelopmental disorders.

$p = 0.044$). The gender difference was seen in the ADHD combined type (21% vs. 7%), and in the ADHD hyperactive/impulsive type (12% vs. 4%), but not in the ADHD inattentive type (26% vs. 24%). Fifty-one of 79 (65 %) were diagnosed with ID at T2. Fourteen participants (18%), almost one in five, had ASD + ADHD at T2 (Table 1).

3.4 | Stability of NDDs

Thirty-four of those 79 (43%) from T1 to T2 had received a diagnosis of ASD, ADHD, or ASD+ADHD at T1. The mean GAF score for this (NDD) at T2 was 46.5 ($SD = 13.1$) compared to 51.4 ($SD = 10.8$) in the non-NDD group (t (77) = 1.826, $p = 0.072$). The majority of those with ASD or ADHD diagnosis at T1 continued to meet criteria for ASD or ADHD at T2. Two participants, one with ASD and one with ADHD at T1, did not meet criteria for those diagnoses at T2. On the other hand, 18 of the 45 participants (40%) who had not been diagnosed with ASD or ADHD met criteria for these disorders at T2 (see Table 2).

3.4.1 | ID at T2

Cognitive assessment at both T1 and T2 had been performed on 55 participants of the total study group. Twenty-one of 27 (78%) continued, according to IQ tests to have ID whereas six with ID who had tested at a level below IQ 70 at T1 scored significantly higher at T2 (≥10 IQ points) and fell within the average range. However, 14 of 28 (50%) who had scored above the ID level at T1 now scored significantly lower and fell within the ID range. One individual tested only at T2 at a level below IQ 70. Twenty-two of the 23 who did not participate in the WAIS test at T2, had been IQ tested at T1 and 15 of these had been diagnosed with ID at T1, meaning that the probable prevalence of ID in this group is 51/79 (65%). Three participants had neither been IQ tested at T1 nor T2, but all three were clinically diagnosed with ID at both assessments meaning that the possible rate of ID in this group is even higher 54/79 (68%).

3.5 | Single and multiple comorbid diagnoses

Of the whole group of 79, only four (5%) had neither ASD, ADHD nor non-NDD psychiatric diagnoses. The vast majority of the 75 with any of these met criteria for more than one diagnosis. Sixteen (20%) had one diagnosis only (NDD = 10, psychiatric diagnoses = 6), whereas 59 (75%) had two or more diagnoses. Twenty of those 24 (83%) with no psychiatric disorder at T2 had ID or NDD (Table 3). Anxiety was significantly more common in the ADHD- compared to the "non-ADHD" group (t (78) = 4.484, $p = 0.043$). Apart from anxiety and comorbid ADHD, there was no significant relationship between other psychiatric disorders and NDD (Table 4).

4 | DISCUSSION

In this longitudinal study of 22q11.2DS and psychiatric and NDDs in 79 adults with 22q11.2DS we found that a majority had NDDs, and/or an intellectual level in the mild ID or the borderline IQ range, indicating serious impairments and difficulties in everyday functioning (also manifested in the low GAF scores found in the study group). These disorders/conditions clearly affect mental health, especially when expectations and demands with age outgrow understanding, adjustment, and support. Of those 23 who did not participate in the WAIS test at T2, 22 had been IQ tested at T1 and 15 of them had ID at T1, meaning that the total prevalence of ID in the group was 51 (65%). This finding was in line with other studies on cognition in adulthood in 22q11.2 deletion syndrome (Green et al., 2009). The stability of ID was strong even though there was a significant "IQ increase" in a small subgroup and a significant "IQ decrease" in a larger subgroup indicating the need for follow-up regarding cognitive ability.

Over the 12–23 years of follow-up, we found overall stability as regards NDD diagnoses. Those who were diagnosed with NDD in childhood continued to a very high degree to meet criteria for any NDD in adulthood. However, a significant subgroup of those who did not receive NDD diagnosis at T1 now met criteria for ADHD, ASD, or a combination of both. This could be partly explained by the fact that some of them were very young at first assessment and that the level

TABLE 3 Psychiatric comorbidity at T2 in 22q11.2DS study group at follow-up.

	No psychiatric disorder	Mood disorder	Anxiety disorder	Psychotic disorder	Mood + anxiety disorder	Mood + psychotic disorder	Anxiety + psychotic disorder	Mood + anxiety + psychotic disorder	Total
No NDD or ID	4 (5)	0 (0)	1 (1)	1 (1)	3 (4)	1 (1)	0 (0)	0 (0)	10 (13)
ASD	1 (1)	1 (1)	4 (5)	0 (0)	2 (3)	0 (0)	0 (0)	1 (1)	9 (11)
ADHD	2 (3)	0 (0)	2 (3)	0 (0)	4 (5)	0 (0)	0 (0)	0 (0)	8 (10)
ID	7 (9)	4 (5)	2 (3)	0 (0)	5 (6)	2 (3)	0 (0)	0 (0)	20 (25)
NDD + ID	10 (13)	4 (5)	6 (8)	2 (3)	6 (8)	2 (3)	0 (0)	2 (3)	32 (41)
Total	24 (31)	9 (11)	15 (20)	3 (4)	20 (25)	5 (7)	0 (0)	3 (4)	79 (100)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; ID, intellectual disability; NDD, neurodevelopmental disorders.

TABLE 4 Psychiatric comorbidity related to autism spectrum disorders, attention deficit/hyperactivity disorder, and intellectual disability.

	ADHD			ASD			Intellectual disability		
	Yes $n = 36$ (%)	no $n = 43$ (%)	p	Yes $n = 28$ (%)	no $n = 51$ (%)	p	Yes $n = 52$ (%)	no $n = 27$ (%)	p
ADHD	…	…	…	14 (50)	22 (43)	0.639	22 (42)	14 (52)	0.480
ASD	14 (39)	22 (51)	0.639	…	…	…	19 (37)	9 (33)	0.810
ID	22 (61)	29 (67)	0.480	18 (64)	33 (65)	0.810	…	…	…
Mood	18 (50)	17 (40)	0.373	12 (43)	23 (45)	1.00	23 (44)	12 (44)	1.00
Anxiety	22 (61)	16 (37)	0.043*	14 (50)	24 (47)	0.818	21 (40)	17 (63)	0.063
Psychotic disorder	4 (11)	7 (16)	0.0746	6 (21)	5 (10)	0.184	8 (15)	3 (11)	0.740
≥ 2 (mo/an/ps)	15 (42)	13 (30)	0.348	9 (32)	19 (37)	0.806	17 (33)	11 (41)	0.621

*$p < 0.05$.

Abbreviations: ADHD, attention deficit/hyperactivity disorder; ASD, autism spectrum disorder; ID, intellectual disability, ≥ 2 mo/an/ps, 2 or more of mood, anxiety and/or psychotic disorder.

of NDD-associated impairments became more striking in adulthood. The prevalence at follow-up of ASD, a third, and ADHD, almost half, were higher compared to the rate in childhood and adolescence. These results differed from the ICBB (Schneider et al., 2014) study where the prevalence of ASD as well as ADHD was lower in the adult group compared to the child and adolescent groups. However, in line with the ICBB study, there was no gender difference for ASD in contrast to ADHD with significantly more males. In our study, this gender difference was seen for the combined and in the mainly hyperactive/impulsive type but not for the mainly inattentive type. Almost one in five of the whole group had ASD + ADHD, with a male predominance.

We found that the prevalence of depressive disorder, 43%, was markedly high compared to the 16% lifetime prevalence reported for the general population (Kessler et al., 2003). More males than females had a history of depression which is not mirrored in the general psychiatric field, where almost twice as many women as men were diagnosed with a depressive disorder (Salk et al., 2017).

The prevalence of bipolar disorder was similar to that in other reports (Schneider et al., 2014) of 22q11.2DS and similar to the general population (Rowland & Marwaha, 2018).

Compared to a 10% lifetime prevalence in the general Euro/Anglo cultures (Baxter et al., 2013), almost half of our group had or had had one or more anxiety disorders, with PD and SAD being the most frequent. Nearly one in five met criteria for OCD compared to 1 in 50 in the general population (Ruscio et al., 2010). Similarly high rates of OCD in 22q11.2DS were found in a study by Gothelf, 33% (Gothelf et al., 2004) compared to 8% in a study by Baker and skuse (2005).

The prevalence of eating disorder was the same as in the general population (Qian et al., 2022), about 1%. We were not able to find any other reports on eating disorders in 22q11.2DS.

None of our participants had symptoms of PTSD which might be explained by the fact that few in this group, had been exposed to severe traumatic situations. No other studies on trauma and PTSD in 22q11.2DS had been published.

Alcohol and substance use disorders were rare in our group similar to other studies in 22q11.2DS (Schneider et al., 2014; Vingerhoets et al., 2019) and occurred at rates lower than in the general population (Glantz et al., 2020; Grant et al., 2016).

None in our group had conduct or antisocial personality disorder, which differs markedly from findings obtained in other groups with high rates of ADHD (with or without ASD), for instance in the

correctional services (Billstedt et al., 2017), but was in line with that of a study of 22q11.2DS + ADHD showing significantly less comorbidity with oppositional defiant disorder and CD compared to those with ADHD without 22q11.2DS (Niarchou et al., 2015).

The prevalence of psychotic symptoms (14%) was lower in our study compared to other reports (20%–40%) of 22q11DS.2 (Gothelf et al., 2013; Murphy et al., 1999; Schneider et al., 2014). Our results were more in line with results from the few existing studies in non-psychiatric clinic contexts (Fung et al., 2010) (Hoeffding et al., 2017). Unlike the general population with a male predominance in psychotic disorders (Blokland et al., 2022), no gender difference was seen in our group, which was similar to what was found in the IBBC study. In our study, only six participants met criteria for schizophrenia spectrum or psychotic disorder. Three had psychotic symptoms during manic or depressive episodes. Two in the group of 11 with any psychotic symptoms had had transient psychotic symptoms during extreme stress and had fully recovered from psychosis. The lower occurrence of psychotic disorders in our group might be explained by methodological differences, but also by early detection of 22q11.2DS as well as early detection of comorbid NDDs, IDs, and psychiatric problems, which enables early and adequate treatment interventions including psychoeducation, adaptations of demands and support and, when needed, pharmaco- and psychological therapies. Although psychosis is a serious condition where antipsychotic treatment is considered necessary, only one in three in the psychosis group received antipsychotics whereas all with schizoaffective symptoms were on mood stabilizers, which suggests that this group is underdiagnosed and undertreated. In contrast to findings from earlier studies (Fiksinski et al., 2017; Vorstman et al., 2013) ASD at baseline was significantly more common in the group that developed psychotic symptoms.

In summary, our results show very high rates of NDDs and other psychiatric disorders. However, we found low or very low rates of psychosis including schizophrenia, when compared with other longitudinal studies of 22q11.2DS.

4.1 | Strengths and limitations

Our study is a unique prospective longitudinal study following a relatively large cohort of individuals with 22q11.2DS, personally assessed, from childhood/adolescence into adult age. It is one of very few studies that evaluated mental health and comorbidity by investigating the whole range of NDDs and psychiatric disorders present at the same time.

Even though our sample size and follow-up rate could be considered exceptionally large for a specific genetic condition clinically examined in great detail, the sample size was probably too small to detect significant differences in many analyses.

The follow-up attrition of 18 individuals (18%) could have affected results, but since there was no difference between non-participants and participants regarding gender, IQ/developmental quotient, or NDD diagnosis with or without comorbidity at T1, we believe that attrition did not have a large impact.

5 | CONCLUSIONS

Adults with 22q11.2DS had very high rates of psychiatric disorders with a majority meeting diagnostic criteria for one or more NDDs with or without comorbid psychiatric disorders. The stability of NDD diagnoses from childhood to adulthood was robust. ASD in childhood was associated with psychotic symptoms in adulthood but at lower rates than in a number of previous publications on 22q11.2DS. Our findings underscore the need for repeated assessments from childhood to adulthood, with a view to better enabling adequate support and demands so as to promote good health, prevent impairment, and optimize intervention effects. It is also important that clinicians in the adult mental health sector always consider the possibility of underlying (undiagnosed) 22q11.2DS in participants presenting with anxiety, mood, psychotic or neurodevelopmental disorders, particularly in those with borderline intellectual functioning or ID.

AUTHOR CONTRIBUTIONS

Christopher Gillberg, Elisabeth Fernell, Carina Gillberg, Eva Billstedt, and Lena Wallin were involved in planning, conceptualization, and design of the study. Eva Billstedt and Lena Wallin acquired the clinical data and conducted the statistical analyses. Lena Wallin wrote the first draft of the manuscript. All authors contributed to and have approved to the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Lena Wallin https://orcid.org/0009-0009-2519-8811

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