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ORIGINAL CONTRIBUTION

Education and employment trajectories from childhood to adulthood in individuals with 22q11.2 deletion syndrome

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Abstract
22q11.2 deletion syndrome (22q11.2DS) is the most common known microdeletion in humans occurring in 1 out of 2000–4000 live births, with increasing numbers of individuals with the microdeletion living into adulthood. The aim of the study was to explore the education and employment trajectories of individuals with 22q11.2DS from childhood to adulthood in a large cohort composed of two significant samples. 260 individuals with 22q11.2DS, 134 male and 126 female, aged 5–59 years (mean age 21.3 ± 10.8 years) were evaluated at two sites, Geneva (GVA) and Tel Aviv (TA). Psychiatric comorbidities, IQ score, and adaptive functioning were assessed using gold-standard diagnostic tools. Demographic factors, such as data about education, employment, marital status, and living status, were collected. Children entering elementary school (5–12 years) were significantly more likely to attend a mainstream school, while adolescents were significantly more likely to attend special education schools ($p < 0.005$). Cognitive abilities, and not adaptive functioning, predicted school placement. Among adults with 22q11.2DS ($n = 138$), 57 (41.3%) were unemployed, 46 (33.3%) were employed in open market employment, and 35 (25.4%) worked in assisted employment. In adulthood, adaptive functioning more than cognitive abilities predicted employment. Surprisingly, psychotic spectrum disorders were not found to be associated with employment. Individuals with 22q11.2DS are characterized by heterogeneity in educational and employment profiles. We found that cognitive abilities and adaptive functioning, and not the presence of psychiatric disorders, are key factors in school placement and employment. These factors should, therefore, be taken into account when planning optimal development of individuals with 22q11.2DS.

Keywords Velocardiofacial syndrome · Education · Adaptive functioning · VABS · Schizophrenia · Psychosis · Employment

Introduction

22q11.2 deletion syndrome (22q11.2DS) is the most common chromosomal microdeletion in humans, occurring in approximately 1 out of 2000–4000 live births [1, 2]. The deletion is associated with high rates of inborn and late-onset features, including congenital heart defects (CHD), intellectual disability (ID) and psychiatric comorbidities [3, 4]. With improvement of medical pediatric care, most children with 22q11.2DS now live to adulthood and integrate into adult life. Main concerns in the management of the syndrome and behavioral display shift during the life span. During childhood, the main concerns include learning difficulties (especially in mathematics and language comprehension) and externalizing behaviors [i.e. impulsivity, oppositionality and attention deficit/hyperactivity disorder (ADHD)]. In adolescence and young adulthood, the main concerns focus on challenges in socialization, including inadequate daily functioning, internalizing behaviors (e.g., withdrawal, anxiety, depression) and increased risk for psychosis [3, 5, 6]. Cognitive deficits are frequently seen, with an average full-scale IQ (FSIQ) score of 75 (borderline range of intelligence) [7] and a tendency for IQ to decline with age [8, 9]. More severe ID is uncommon in the 22q11.2DS population [9]. These cognitive deficits are likely to impact daily activities, learning abilities and living skills. Additionally, high level of anxiety and impairment in social functioning (i.e.

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deficits in communication, difficulty initiating and sustaining social relationships), are common in 22q11.2DS individuals across all ages [10], may affect functioning in school and adaptation to workplace.

Children with 22q11.2DS may begin to experience difficulties only in later elementary school years (3–4th grade), when the educational focus begins to shift from concrete to more abstract thinking such as mathematical reasoning and reading comprehension [11]. Integration and inclusion in mainstream education of children with 22q11.2DS may play a role for such individuals to later assimilate into society. Conversely, segregation, which allows for children with special needs to be educated in separate special education classes or special education schools, does not promote such assimilation. According to the European Agency for Development in Special Needs Education 2% to over 14% of students in the European countries included in the Agency are recognized as having special needs, and between 0.5% and over 5.5% are educated in segregated settings [12]. A survey conducted in the UK stated that 74% of children with 22q11.2DS were reported as having a statement of special educational needs [13]. Of these, 76% percent were integrated in mainstream schools, 16% were in special education schools, 5% were in private schools and 4% were attending other school types.

Employment is one of the life areas in which adults with ID and psychiatric comorbidities may experience difficulties in integration. For example, employment rates of adults with ID vary between 25 and 40% in Canada [14]. People with ID in the Canadian work force are about six times more likely than other people without disabilities or people with different types of disability, to have never worked [14]. Employment rates also vary by psychiatric diagnostic clusters, e.g., individuals with a major depressive disorder have an employment rate of 40–60%, while those individuals with anxiety disorders have an employment rate of 20–35% [15]. Employment rates among those with schizophrenia are only 10–20% [15]. Moreover, some of the 22q11.2DS individuals with psychiatric comorbidities receive pharmacological treatment, which is suggested to impact functioning. Treatment with atypical antipsychotics [16] and methylphenidate [17] among children with ID was found to improve ADHD symptoms, social relationships and occupational abilities.

One study conducted in Canada that assessed functional outcomes of adults ($n = 100$) with 22q11.2DS found that the majority of adults (66%) in the study were employed, regardless of cognitive functioning and psychotic comorbidity. They further found low rates for sheltered employment (5%). Only a minority of the sample, however, was financially independent of either family or government sources [18]. Another small scale study in USA ($n = 30$) found 35% employment rates for adults with 22q.11.2DS [19]. To our knowledge, no studies in other countries or cultures have been undertaken, as yet, of employment rates of adults with 22q11.2DS.

There are very limited data evaluating school education, employment and independent living with regard to individuals with 22q11.2DS over the life span. Exploring social, academic and occupational functioning is important to inform expectations of affected individuals, their families and clinicians. This will enhance the understanding of social and adaptive functioning profiles in the 22q11.2DS population. Knowing the strengths and weaknesses of individuals with 22q11.2DS in the social and daily functioning environments may help plan appropriate educational and employment careers to obtain more favorable outcomes for individuals with 22q11.2DS.

The aim of the current study was to explore the academic trajectory and occupational outcomes of individuals with 22q11.2DS from childhood to adulthood, in a large cohort composed of two samples from different countries in Europe and Israel. We focused on two main stages: (1) education and academic achievements during childhood and adolescent years; and (2) adult life focusing on employment, living situation and marriage.

We hypothesized that there would be an association between lower cognitive abilities and both lower adaptive functioning and higher prevalence of psychiatric disorders to the rate of children and adolescents studying in special education schools. In adulthood, we hypothesized that individuals employed in the open market and live independently will present with higher intellectual level, higher adaptive functioning scores and lower rates of psychiatric comorbidities, primarily psychotic spectrum disorders compared to those who worked in assisted employment and those who were unemployed.

Methods

Participants

The sample consisted of 260 individuals with 22q11.2DS, 134 males and 126 females, aged 5–59 years (mean age 21.3 ± 10.8 years) that were evaluated at two sites, Geneva (GVA) and Tel Aviv (TA). The TA cohort comprised of 142 individuals with 22q11.2DS, 79 males and 63 females (mean age 23.5 ± 11.9 years). Participants were recruited from the Behavioral Neurogenetics Center, Sheba Medical Center (Tel Hashomer, Israel). The center is unique in Israel, treating individuals with 22q11.2DS with referrals from all over the country. The GVA cohort comprised 118 individuals with 22q11.2DS, 55 males and 63 females (mean age 18.5 ± 8.4 years). Participants were recruited through announcements to parent associations in Switzerland, France, and French-speaking Belgium.

The diagnosis of 22q11.2DS was confirmed using an array of comparative genomic hybridization and/or fluorescence in situ hybridization (Vysis, Downers Grove, IL, USA) or multiplex ligation-dependent probe amplification [20]. The Institutional Review Board of Sheba Medical Center and the Centralized Ethics Commission in Switzerland approved the research protocols. Written informed consent was obtained from participants and their parents in both cohorts.

Table 1 compares the demographic and clinical characteristics of TA and GVA samples. The two samples matched for most variables including sex distribution and rates of the various psychiatric disorders. They differed in age, as the TA sample was significantly older (23.5 ± 11.9 vs. 18.5 ± 8.4 years; $t(258) = 3.9$; $p < 0.0005$) and FSIQ (74.4 ± 12.3 vs. 70.4 ± 12.7; $t(245) = 2.48$; $p = 0.014$) (Table 1).

Psychiatric assessment

TA cohort

Trained clinicians used the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL) to interview all subjects and their parents [21]. If an affirmative response was given to any symptom category from the screening interview, the related K-SADS module was administered. The adult participants and their parents were interviewed using the Structured Clinical Interview for Axis I DSM-IV (SCID) [22]. The ADHD items from the K-SADS were added to the SCID to evaluate the presence of ADHD in adults with 22q11.2DS.

Table 1 Comparison of demographic and clinical characteristics between the Tel Aviv and Geneva cohorts

	All ($n = 260$)	Tel Aviv ($n = 142$)	Geneva ($n = 118$)	Statistics
Age (mean ± SD; years)	21.3 ± 10.8 (5–59)	23.5 ± 11.9 (6–59)	18.5 ± 8.4 (5–48)	$t(258) = 3.9$; $p < 0.0005$
Male/female %	134/126 (51.5/48.5)	79/63 (44.4/55.6)	55/63 (46.6/53.4)	NS
Cognition				
FSIQ	72.5 ± 12.6 (42–120)	74.4 ± 12.3 (45–120)	70.4 ± 12.7 (42–108)	$t(245) = 2.48$; $p = 0.014$
VIQ	75.5 ± 12.7 (45–125)	76.4 ± 11.0 (52–125)	74.7 ± 13.8 (45–106)	NS
PIQ	72.9 ± 12.8 (46–118)	74.5 ± 13.3 (47–118)	71.8 ± 12.3 (46–110)	NS
Adaptive functioning (VABS)				
ABC	71.2 ± 17.4 (19–107)	71.9 ± 18.3 (20–107)	69.7 ± 15.4 (19–95)	NS
Communication	71.6 ± 18.4 (21–108)	71.0 ± 19.5 (21–106)	72.8 ± 15.9 (21–108)	NS
Daily-living skills	72.4 ± 18.7 (20–121)	73.4 ± 21.1 (20–121)	70.5 ± 12.5 (37–96)	NS
Socialization	77.6 ± 18.1 (20–125)	78.3 ± 18.8 (20–125)	76.0 ± 16.8 (20–121)	NS
Psychiatric disorders	177 (68.1)	121 (85.2)	56 (47.5)	
Psychotic disorders (any)	29 (11.2)	20 (14.1)	9 (7.6)	NS
Schizophrenia	17 (6.5)	13 (9.2)	4 (3.4)	
Schizoaffective disorder	6 (2.3)	3 (2.1)	3 (2.5)	
Schizophreniform disorder	1(0.4)	0	1 (0.8)	
Brief psychotic disorder	2 (0.8)	2 (1.4)	0	
Psychotic disorder NOS	1 (0.4)	1 (0.7)	0	
Affective disorders (any)	44 (16.9)	29 (20.4)	15(12.7)	NS
MDD	39 (15.0)	25 (17.6)	14 (11.9)	
Dysthymia	8 (3.1)	7 (4.9)	1 (0.8)	
Bipolar disorder	1 (0.4)	1 (0.7)	0	
Anxiety disorders (any)	93 (35.8)	49 (34.5)	44 (37.3)	NS
GAD	42 (16.2)	22 (15.5)	20 (16.9)	
Social phobia	23 (8.8)	16 (11.3)	7 (5.9)	
Specific phobia	61 (23.5)	30 (21.1)	31 (26.3)	
OCD	13 (5.0)	8 (5.6)	5 (4.2)	NS
ADHD	104 (40.0)	77 (54.2)	27 (22.9)	NS

NS not significant, *FSIQ* full-scale intelligence quotient, *PIQ* performance intelligence quotient, *VIQ* verbal intelligence quotient, *VABS* Vineland adaptive behavioral scale, *ABC* adaptive behavior composite, *MDD* major depressive disorder, *GAD* generalized anxiety disorder, *OCD* obsessive compulsive disorder, *ADHD* attention deficit/hyperactivity disorder

GVA cohort

The presence of psychiatric disorders was evaluated in adolescents below 18 years using the Diagnostic Interview for Children and Adolescents—Revised [23] and the mood and psychosis supplement of the K-SADS-PL. Adult participants were screened using the SCID. ADHD was evaluated only in participants < 18 years.

Cognitive and adaptive functioning assessment

Cognitive evaluation in both centers was performed by well-trained, masters-level psychologists using the age appropriate versions of the WISC-III [24] or IV [25] and WAIS-III or WAIS-R [26]. Adaptive functioning was assessed using the Vineland Adaptive Behavior Scale-I or II (VABS) [27], a semi-structured interview conducted with the parent or the primary caregiver of the participant. The VABS provides age-adjusted standardized scores in the domains of communication, daily living and socialization skills [28]. An adaptive behavior composite (ABC) score, a measure of global adaptive functioning of the individual, is calculated from these three domains. For participants above age 18 years, we used the norms of the upper age level as suggested by the VABS manual.

Academic and occupational assessment

Information about education and occupation were obtained in both centers between January 2000 and June 2017 using a semi-structured interview covering detailed data about the number of years and type of education, living situation, and about the type of occupation. Data were not complete for all variables collected for all subjects, see Tables 1, 2, 3, 4 and 5 for details.

Education

Assessment of education was undertaken only in school-aged individuals (up to 21 years old). Based on the collected information, individuals were divided into four education groups as follows: (1) mainstream class in a mainstream school. (2) Mainstream school with assistance. We included two types of assistance—additional time during exams and personal assistance, namely, a shadow. A shadow is a person who assists the child during school hours by providing a bridge in social communication with other children, provides physical assistance if needed and specific educational assistance during class. The nature of the assistance and the amount of hours depends on the type of disability and the child's personal needs. In Israel, shadows are provided by the State to individuals diagnosed as having a significant disability (cerebral palsy or other physical disabilities, blindness or visual impairment, autistic spectrum disorder or other severe psychiatric disorders). The same criteria for personal assistance exist in France, but not in Belgium or Switzerland. (3) Special education class in a mainstream school. In Israel, a special education class belongs to the special education system, but is located in a mainstream school, thus applying the principle of integration. A special education class is a small class, comprising up to 12 students, thereby allowing teachers to treat each student according to his or her academic and social needs. A therapeutic team, offering personalized therapies (usually art, drama, music, etc.), also works in these classes. The special education framework is divided into the following classes: learning disabilities, behavioral difficulties and communication difficulties. We referred to each of the three groups as a special education class. There are also special education classes in mainstream schools in France, Switzerland and Belgium, applying the same principles of integration. (4) Special education schools. These schools educate children and adolescents with special needs including physical, psychiatric, emotional-behavioral problems, sensory, cognitive or language impairment or ID and are independent of mainstream schools. Children study in small classes, and receive accompanying services including medical and paramedical treatments according to their needs.

In the Israeli education system, children enter school at the age of 6 with mainstream schools providing education until the age of 18 and special education schools providing education until age 21. In Switzerland, mainstream education begins at the age of 4 and ends at age 16; in France, mainstream education begins at the age of 3 and ends at 16 years, whereas in Belgium it begins at age 6 and ends at age 15. In these three latter countries, special education classes begin at age 6 and ends at age 18. For individuals who transferred during their schooling between different types of education systems, we addressed them in our analyses based only on their current education.

Occupation

This information was assessed only in adults (> 18 years). Occupation was divided into three main groups: (1) regular employment. Working in an open market workplace. Those who were currently employed were asked about place of employment. (2) Assisted employment. This refers to a setting offered to individuals with disabilities who are not capable of working in an open market workplace They receive services and training in a variety of assisted or supported jobs. (3) Unemployed. Unemployed individuals were asked if they were looking for training or for a job; were too disabled to work (either stay at home or have social group or other therapy during the day); have difficulties in maintaining a job; or were institutionalized in a mental health

Table 2 Educational characteristics of the study sample ($n=132$)

	5–12 years ($n=57$)	13–16 years ($n=41$)	17–21 years ($n=34$)	Statistics
(a) Comparison of distribution of type of education among the age groups				
Age (±SD)	9.2 ± 2.1	14.2 ± 1.2	18.3 ± 1.1	
Male/female %	35/22 61.4/38.6	19/22 46.3/53.7	22/12 64.7/35.3	NS
Education				
Mainstream class in a mainstream school	11 (19.0)	7 (17.1)	10 (29.4)	NS
Mainstream school with assistance	27 (46.6)	11 (26.8)	7 (20.6)	$\chi^2=8.2$; $df=2$; $p=0.017$
Special education class in a mainstream school	16 (27.6)	15 (36.6)	5 (14.7)	NS
Special education school	3 (5.2)	8 (19.5)	12 (35.3)	$\chi^2=13.5$; $df=2$; $p=0.001$

	Mainstream class in a mainstream school ($n=28$)	Mainstream school with assistance ($n=45$)	Special education class in a mainstream school ($n=36$)	Special education school ($n=23$)	Statistics				
					ss	*df*	*F*	*p* value	Post hoc
(b) Comparison of clinical characteristics among type of education									
Age	13.9 ± 3.8 (7–20)	11.6 ± 4.1 (5–20)	12.2 ± 3.8 (6–18)	15.5 ± 3.5 (6–21)	384.8	3	9.21	< 0.005	Groups IV > groups II, III
Male/female%	16/12 57.1/42.9	23/22 51.1/48.9	22/14 61.1/38.9	15/8 65.2/34.8				NS	
Cognition									
FSIQ	81.2 ± 12.0 (63–108)	73.9 ± 12.0 (52–115)	68.9 ± 11.9 (47–102)	69.8 ± 12.5 (42–104)	2720.1	3	6.2	0.001	Group I > groups III, IV
VIQ	85.8 ± 10.6 (69–106)	79.2 ± 10.9 (57–100)	72.0 ± 12.6 (45–96)	72.0 ± 11.8 (52–100)	3047.7	3	7.8	< 0.0005	Group I > groups III,IV
PIQ	81.4 ± 14.4 (58–118)	73.0 ± 10.3 (55–96)	68.5 ± 13.0 (51–118)	72.4 ± 13.4 (53–108)	2130.2	3	4.6	0.005	Group I > group III
Adaptive functioning (VABS)									
ABC	77.6 ± 10.2 (59–95)	75.3 ± 11.4 (54–95)	71.3 ± 14.3 (19–89)	71.9 ± 11.6 (51–89)	384.0	3	0.85	NS	
Communication	79.4 ± 11.1 (61–104)	78.0 ± 13.5 (55–108)	75.2 ± 7.5 (65–98)	72.5 ± 12.2 (47–91)	406.5	3	1.08	NS	
Daily-living skills	77.0 ± 15.6 (64–121)	73.9 ± 11.1 (51–96)	71.6 ± 12.6 (37–95)	72.1 ± 12.2 (45–97)	248.7	3	0.46	NS	
Socialization	82.2 ± 16.1 (54–125)	81.8 ± 14.5 (55–121)	80.3 ± 11.7 (50–104)	78.7 ± 11.7 (60–95)	108.1	3	0.20	NS	
Psychiatric diagnoses									
Any psychiatric diagnosis	16 (57.1)	25 (55.7)	26 (72.2)	19 (82.6)				NS	
Any psychosis	0 (0)	0 (0)	1 (2.8)	2 (8.7)				NS	
Any mood	2 (7.1)	6 (13.3)	3 (8.3)	1 (4.3)				NS	
Any anxiety	9 (32.1)	19 (42.2)	15 (41.7)	11 (47.8)				NS	
ADHD	15 (53.6)	19 (42.2)	21 (58.3)	10 (43.8)				NS	

NS not significant, *FSIQ* full-scale intelligence quotient, *PIQ* performance intelligence quotient, *VIQ* verbal intelligence quotient; *VABS* Vineland adaptive behavioral scale, *ABC* adaptive behavior composite; *ADHD* attention deficit/hyperactivity disorder

facility. Those currently employed and those who were unemployed but had worked previously were asked about past employment. In the TA cohort, individuals older than 18 years, who were currently in the army or still studying in special education schools was excluded from the employment analysis.

To assess social functioning, level of integration into society and independence, adult individuals with 22q11.2DS

Table 3 Multinomial logistic regression model predicting type of education

	Special education school ($n=23$)		Mainstream school with assistance ($n=54$)		Special education class in a mainstream class ($n=36$)	
	OR	95% CI	OR	95% CI	OR	95% CI
Age	1.17	0.32–4.35	**0.29***	**0.08–1.02**	0.58	0.16–2.10
FSIQ	**0.92***	**0.81–1.03**	**0.90****	**0.83–0.98**	**0.86*****	**0.78–0.94**
VABS ABC	0.99	0.90–1.09	1.02	0.93–1.11	1.00	0.92–1.10
Any psychiatric diagnoses	5.61	0.43–73.5	1.93	0.28–13.36	1.65	0.19–13.83

Significant results are in bold

FSIQ full-scale intelligence quotient, *VABS ABC* Vineland adaptive behavioral scale, Adaptive Behavior Composite

*$p<0.05$

**$p<0.001$

***$p<0.0001$

were further asked about: living situations—living with parents or family members; living alone; living with a partner or a flat mate; living in a specialized institution; driving license ownership; marital status—single or married (including those are divorced, widowed or in a committed relationship).

Statistical analysis

Statistical analysis was conducted using IBM Statistical Package for the Social Sciences (SPSS) v. 20 for Windows (IBM Inc, Chicago, IL, USA). To examine the trajectories of education across life, the cohort was divided into three age groups: 5–12 years ($n=57$, mean age 9.2 ± 2.1 years); 13–16 years ($n=41$, mean age 14.2 ± 1.2 years); 17–21 years ($n=34$, mean age 18.3 ± 1.1 years). To examine the trajectories of employment, the adult cohort was divided into three age groups: 18–21 years ($n=42$, mean age 19.1 ± 1.0 years); 22–25 years ($n=39$, mean age 23.5 ± 1.1 years); older than 25 years ($n=72$, mean age 35.4 ± 7.5 years).

Standard statistical tests were used for between- and within-group comparisons, that is, Student *t* test for continuous variables, and Pearson's x^2 test or Fisher's exact test for categorical variables. Analysis of variance (ANOVAs) was used to identify group differences with regard to cognition (FSIQ, verbal IQ, and performance IQ) and adaptive functioning scores (VABS ABC, communication, daily living skills and socialization). Education and employment types were held as a fixed factor. Post hoc tests were used to assess the individual regression coefficients.

Multinomial logistic regression is designed for modelling categorical outcome variable with more than two categories. We performed two multinomial logistic regression models. The first aimed to predict allocation into one of the education types (Table 3). The omitted comparison category in the model was the mainstream school mainstream class ($n=28$) and the model predicted the likelihood that individuals would attend a mainstream school with assistance ($n=45$), special education class in a mainstream school ($n=36$), and special education school ($n=23$). Age, FSIQ, VABS ABC score and any psychiatric diagnosis were chosen as predictive variables. The second model aimed to predict employment (Table 5). The omitted comparison category in the model was employment in the open market place ($n=46$) and the model predicted the likelihood that individuals would be unemployed ($n=57$) or in assisted employment ($n=35$). The same predictive variables were chosen as in the education model.

Results

Education

Of the entire sample, 132 individuals (50.8%) were currently attending school at the time of testing. Children in elementary school (5–12 years) were significantly more likely to attend a mainstream school with assistance compared to those aged 13–16 years ($x^2=4.41$, $df=3$, $p=0.004$) and those aged 17–21 years ($x^2=6.52$, $df=3$, $p=0.011$). An opposite trend was observed for rates of children in special education, with significantly less younger children (aged 5–12) attending special education schools ($n=3$, 5.2%) compared to adolescents (aged 13-16, $x^2=4.91$, $df=3$, $p=0.028$) and to those aged 17–21 ($x^2=13.94$, $df=3$, $p<0.0005$) (Table 2a).

In line with these results, Table 2b shows that individuals attending special education schools are significantly older compared to those in mainstream schooling with assistance and in special education classes in mainstream schooling (15.5 ± 3.5 years vs. 12.2 ± 3.8 years and 11.6 ± 4.1 years, respectively, $p<0.0005$). Among the 36 individuals studying in special education classes located in mainstream schools,

Table 4 Employment characteristics of the study sample ($n=153$)

	18–21 years ($n=42$)	22–25 years ($n=39$)	> 25 years ($n=72$)	Statistics
(a) Comparison of distribution of employment, living situation and marriage among age groups				
Age (± SD)	19.1 ± 1.0	23.5 ± 1.1	35.4 ± 7.5	
Male/female%	26/16 61.9/38.1	14/25 35.9/64.1	32/40 44.4/55.6	NS
Employment				
Unemployed	18 (42.8)	13 (33.3)	26 (36.1)	NS
Still at school	4 (9.5)			
Currently employed	7 (16.7)	13 (33.3)	26 (36.1)	$\chi^2=5.04$; $df=2$; $p=0.08$
Assisted employment	6 (14.3)	10 (25.6)	19 (26.4)	NS
Living situation				
With parents or family members	39 (92.9)	27 (69.2)	22 (30.6)	$\chi^2=62.8$; $df=2$; $p<0.0005$
Alone	0	4 (10.3)	13 (18.1)	$\chi^2=8.78$; $df=2$; $p=0.012$
With partner/flat mate	1(2.4)	5 (12.8)	21 (29.2)	$\chi^2=13.93$; $df=2$; $p=0.001$
Specialized institution	2 (4.8)	3 (7.7)	15 (20.8)	$\chi^2=7.36$; $df=2$; $p=0.025$
Married/committed relationship	0	2 (5.1)	27 (37.5)	$\chi^2=30.7$; $df=2$; $p<0.0005$

	Regular employment ($n=46$)	Assisted employment ($n=35$)	Unemployed ($n=57$)	Statistics				
				ss	*df*	*F*	*p* value	Post hoc
(b) Comparison of clinical characteristics among types of employment								
Age (± SD)	29.7 ± 8.4 (18–47)	27.8 ± 6.3 (19–43)	28.4 ± 10.9 (18–59)				NS	
Male/Female %	19/27 41.3/58.7	17/18 48.6/51.4	31/26 54.4/45.5				NS	
Cognition								
FSIQ	74.9 ± 9.5 (49–94)	67.3 ± 12.8 (46–97)	68.3 ± 11.3 (42–94)	1401.6	2	5.6	0.005	Group I > group II, III
VIQ	77.6 ± 10.3 (54–102)	67.3 ± 11.2 (49–90)	71.9 ± 10.2 (52–98)	1747.3	2	7.9	0.001	Groups I > group II, III
PIQ	76.0 ± 10.6 (53–106)	66.3 ± 9.4 (46–82)	71.2 ± 12.5 (47–96)	1522.3	2	6.2	0.003	Group I > group II
Adaptive functioning								
ABC	79.4 ± 15.8 (34–107)	63.6 ± 20.3 (33–103)	63.7 ± 19.3 (20–98)	2836.9	2	8.5	< 0.0005	Group I > groups II, III
Communication	79.4 ± 15.8 (33–106)	61.2 ± 23.6 (21–96)	61.6 ± 19.6 (21–94)	7358.5	2	10.0	< 0.0005	Group I > groups II, III
Daily-living skills	81.0 ± 18.6 (25–107)	65.4 ± 22.2 (20–100)	65.4 ± 20.5 (21–107)	5593.5	2	6.9	0.002	Group I > groups II, III
Socialization	85.0 ± 15.8 (48–111)	63.6 ± 20.3 (35–106)	70.0 ± 21.1 (20–100)	5556.4	2	7.9	0.001	Group I > groups II, III
Psychiatric diagnosis								
Any psychiatric diagnosis	36 (78.3)	23 (65.7)	41 (71.0)				NS	
Any psychosis	5 (10.9)	8 (22.9)	14 (24.6)				NS	
Any mood	14 (30.4)	5 (14.3)	12 (21.1)				NS	
Any anxiety	20 (43.5)	9 (25.7)	19 (33.3)				NS	
Living situation								
With family members	20 (43.5)	19 (54.3)	38 (66.7)				NS	
Alone	8 (17.4)	4 (11.4)	4 (7.0)				NS	
With partner/flatmate	14 (30.4)	4 (11.4)	8 (14.0)	$\chi^2=6.16$; $df=2$; $p=0.046$				
Specialized institution	4 (8.7)	8 (22.9)	7 (12.3)				NS	
Driver's license	12 (26.1)	4 (11.4)	5 (8.8)	$\chi^2=6.44$; $df=2$; $p=0.04$				
Married/committed relationship	17 (37.0)	1 (2.9)	11 (19.3)	$\chi^2=14.09$; $df=2$; $p=0.001$				

NS not significant, *FSIQ* full-scale intelligence quotient, *PIQ* performance intelligence quotient, *VIQ* verbal intelligence quotient, *ABC* adaptive behavior composite

Table 5 Multinomial logistic regression model predicting employment ($n=116$)

	Unemployed ($n=57$)		Assisted employment ($n=35$)	
	OR	95% CI	OR	95% CI
Age	0.98	0.92–1.04	0.99	0.93–1.07
FSIQ	0.97	0.91–1.02	1.02	0.96–1.09
VABS ABC	**0.96***	**0.92–0.99**	**0.93****	**0.89–0.97**
Any psychiatric diagnoses	0.58	0.14–2.33	0.25	0.06–1.11

Significant results are in bold

FSIQ full-scale intelligence quotient, *VABS ABC* Vineland adaptive behavioral scale, Adaptive Behavior Composite

*$p<0.05$

**$p<0.001$

9 individuals (25%) received some inclusion hours in a mainstream class. In 9 (20%) of the 45 children attending mainstream schools with assistance, the assistance comprised only additional time for exams. In the rest of the cases ($n=36$), a shadow was present in the class. In total, 43 individuals (32.5%) repeated at least one grade.

Individuals attending a mainstream class in a mainstream school had significantly higher FSIQ, VIQ and PIQ scores compared to all other education types. Individuals attending mainstream schools also presented with higher VABS scores in all domains compared to those attending special education schools. In terms of psychiatric diagnoses, individuals attending a mainstream class in a mainstream school had lower rates of any psychiatric comorbidities compared to those in special education schools, this trend was marginally significant ($x^2=3.80$, $df=1$, $p=0.05$) (Table 2b). There were no significant differences in terms of specific psychiatric diagnoses between education types.

To test which variables differ among education types, we conducted a multinomial logistic regression with special education school, mainstream school with assistance and special education class in a mainstream school as the outcome measure. Potential predictors in the model were FSIQ, VABS ABC scores, and any psychiatric diagnosis. The regression model predicted a significant association between FSIQ and the type of education. Furthermore, age was associated with significantly higher odds of studying in a mainstream school with assistance (Table 3).

Employment

Rates of employment, assisted employment and unemployment are presented in Table 4a. Types of job held are shown in supplementary Table 1. Individuals aged > 25 years were more likely to be employed compared to those aged 18–21 years ($n=26$, 36.1% vs. $n=7$, 16.6%; $x^2=4.87$, $df=1$, $p=0.027$) (Table 4b).

Figure 1 compares main reasons for unemployment when allocating individuals who were unemployed into two age groups. In general, self-reports about disability (intellectual or physical) characterized the unemployment group ($n=17$, 29.8%). Significantly, more unemployed individuals in the younger age group (18–25 years) reported that they were looking for a job or for training compared to the older age group (> 25 years) ($n=11$, 55% vs. $n=5$, 15.6%, respectively; $x^2=8.65$, $df=1$, $p=0.003$). Significantly, more unemployed individuals from the older group (> 25 years) reported being too disabled to work or being institutionalized ($n=8$, 40% vs. $n=22$, 68.8%; $x^2=4.17$, $df=1$, $p=0.041$). There were no significant differences in the rates of psychotic disorders, mood or anxiety disorders between the younger and older groups. About one-fifth of the currently unemployed individuals had been previously employed ($n=20$, 27.0%).

Individuals holding a job in the open market had significantly higher cognitive abilities compared to those in assisted employment (Table 4b). Furthermore, those who were employed in open market settings had significantly higher rates of driving license ownership compared to those who were unemployed ($x^2=5.54$, $df=1$, $p=0.019$). A larger proportion of employed individuals were married compared to individuals with assisted employment or no employment ($\chi^2=14.09$; $df=2$; $p=0.001$).

A second multinomial logistic regression model, to test which variables differ among employment types, was conducted. Unemployment and assisted employment were outcome measures, and age, FSIQ, and VABS ABC scores were potential predictors. The regression model predicted that adaptive functioning as assessed by VABS ABC score were predictive of employment, and not FSIQ (Table 5). A trend was observed between any psychiatric diagnoses and working in assisted employment (OR = 0.25, CI 95% 0.06–1.11, $p=0.06$).

Discussion

Educational and employability concerns are frequently reported in 22q11.2DS individuals and their families. A prominent concern of parents and caregivers is the impact of the 22q11.2DS on children's functionality. To our knowledge, this is the first study to use a large sample, ranging from childhood to adulthood, that reports educational and employment trajectories from two cohorts with different cultural backgrounds.

The results of the present study show that overall cognitive abilities predict the type of education system in which

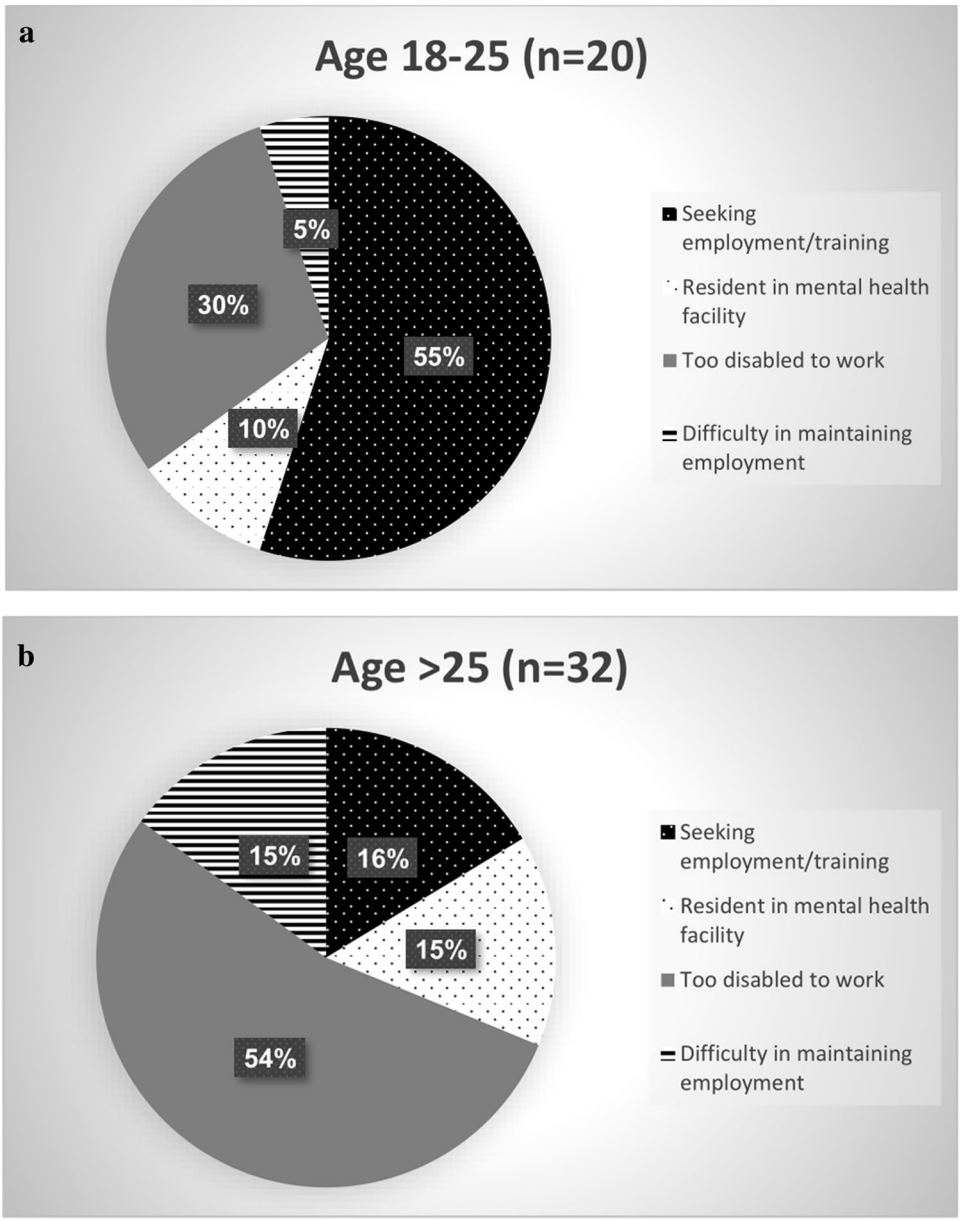

Fig. 1 Characteristics of older and younger unemployed 22q11.2DS adults. **a** Younger, **b** older

children will study to a greater extent than level of adaptive functioning. In adulthood, more than half of 22q11.2DS individuals were employed (either in an open market job or assisted employment). As individuals with 22q11.2DS mature, adaptive functioning, more than cognitive abilities are predictors of employment.

Cognitive abilities play a key factor in determining whether children and adolescents with 22q11.2DS will enter mainstream education (with or without additional assistance) or special education that is adapted to their individual needs. In the present study, most children were attending mainstream education at the beginning of elementary school (age 5–12 years), and only a minority of children were attending special education schools. In high school, a reverse tendency was detected, with most children studying in special education frameworks (either special education class or special education school). The negative association between age and cognitive abilities described in individuals with 22q11.2DS, particularly a decline in verbal IQ [9, 29], but also in FSIQ [30], may explain the change in education with age. Longitudinal studies [31, 32] have shown that different cognitive trajectories can be observed in individuals with 22q11.2DS. Some children present with a stable IQ trajectory with suitable progress to keep up with the gradual increase of the level of academic/educational requirements; in some cases, a decrease in IQ score with a growing deficit is observed, leading to an increasing discrepancy compared to the age-required norms.

Given the presence of various cognitive trajectories over time and the possible decline in IQ scores, we recommend that cognitive abilities of children and adolescents with 22q11.2DS be periodically evaluated especially before transition to new schools (e.g. at transitions from elementary school to middle school and from middle school to high school). From our experience, children benefit by attending schools that are suitable to their cognitive abilities. When school demands are higher than the child's academic abilities, the academic gap widens and the child feels frustrated and discouraged from studying and progressing academically. Adjusting the learning environment and the expectations of a child's family to the child's cognitive abilities helps the child maximize his academic potential.

We found that the presence of any psychiatric disorder, but not specific psychiatric disorders, differs between those attending mainstream school in a mainstream class and those in special education schools. However, this association did not remain strong after the regression analysis. Consistent with the literature, in the present study the two most common psychiatric disorders in children and adolescents with 22q11.2DS were ADHD (40.0%) and anxiety disorders (35.8%) [3]. ADHD has long been suggested to affect functioning and quality of life of affected individuals [33]. Inattentive symptoms including short attention span, difficulty organizing tasks and activities, forgetfulness, and a tendency to lose things, are more pronounced in 22q11.2DS population than in non-22q11.2DS individuals [34]. Despite the high prevalence of ADHD, only about one-third of individuals are treated [35]. A child with ADHD and 22q11.2DS that is untreated has difficulty sitting through class and may experience poor learning progression. Thus, from our clinical experience, treating ADHD in children with 22q11.2DS is important to maximize the learning potential of these children.

Anxiety disorders are another major factor that negatively affects functioning in children with 22q11.2DS. It was found that anxiety symptoms, more than IQ, negatively correlate with adaptive functioning and everyday living skills in children with 22q11.2DS [36]. Therefore, early identification and treatment of anxiety symptoms in children with 22q11.2DS are probably also important for improving functioning in school.

About 25% of individuals develop psychotic spectrum disorders by the age of 25 years [3]. In the present study, three individuals with psychosis were studying in the special education system, and none were in the mainstream education system. We believe that we found significant association between type of school system and the presence of psychiatric disorder, but not any specific psychiatric disorders because of power issues related to the sample size.

Notably, in the present study, adaptive functioning was found to be unrelated to the type of education. Adaptive functioning refers to the functioning skills and behaviors that allow individuals to cope with daily-living demands. This supports a common notion about school, namely, that school provides academic skills such as reading, writing and mathematics, skills that are more prominently affected by IQ level than from adaptive functioning.

Whereas adaptive functioning was unrelated to education type, it showed significant influence on employment status in 22q11.2DS. In the present study, 58% of 22q11.2DS adults were employed in an open market ($n=46$, 33.3%) or assisted employment environment ($n=35$, 25.4%). Previous studies in 22q11.2DS have shown similar employment rates [19, 37], whereas other study showed higher rates [18]. The discrepancy in the employment rates among studies may be due to the different social systems in the different countries, as a great proportion of our cohort were working in assisted employment settings which may be less accessible in some countries. Cognitive impairments may have some negative impact on functioning, as we found some association between IQ and employment, but the regression analysis showed IQ had less significant effect than adaptive functioning, consistent with the literature [18]. Adaptive functioning such as communication, daily living skills (independent living, financial management) and socialization are skills that are essential for employment and adult functioning. Employed individuals had higher rates of marriage, consistent with our previous finding that adaptive functioning, more than cognitive ability, is associated with marriage in 22q11.2DS adults [38].

Integration into employment is an important challenge facing young adults in general and youth with disabilities, in particular. In the present study, 38.3% of the young adults (>25 years) were unemployed and more than half of them were looking for a job or job training. Our results are in line with data that show higher unemployment rates of young adults with intellectual or physical disabilities in their early career compared to their nondisabled peers [39, 40].

Individuals with 22q11.2DS cope with several challenges that may affect their abilities to incorporate into the employment market, mainly in early career years. In addition to cognitive and adaptive functioning deficits, potential obstacles for employment encountered by 22q11.2DS adults' lack of work experience are limited access to post-school education and training, and stigma and discrimination [41], and the debilitating effect of the comorbidity with schizophrenia.

Contrary to our hypothesis, in the present study no association was found between employment and psychotic spectrum disorders and no association with mood and anxiety disorders. This may be due to the high rates of individuals working in assisted employment that provides safe environments adjusted to the individual's capabilities and disabilities and thus are not in the unemployment group.

To improve adult outcomes in the fields of financial management, employment and overall daily functioning, it

may be helpful to establish intervention techniques, already during late adolescence, with shift in focus from academic curriculum to training for work and daily living skills that foster independence. For example, a team-based treatment program that included high levels of supported employment and education services for individuals with first-episode psychosis was shown to be associated with greater improvement in school and employment participation [42].

The strengths of the current study include a large sample composed of multi-site and several countries which allow increased generalizability. Though the education systems in the participating countries were different, we strove for standardization and thus were able to compare them. The main limitation of the study is its retrospective and cross-sectional nature. As such, we were unable to identify predictive factors for education and employment status over time. Further, large-scale longitudinal studies may better help to identify individual factors that could impact education and employment. Furthermore, the impact of each psychiatric diagnosis (ADHD, psychotic, anxiety and mood disorders) was difficult to establish because of the limited number of individuals affected by each condition. Environmental variables, such as parental support, were not studied in the present study but could also moderate the influence of cognitive abilities and psychiatric condition on education and employability status. In the current study, we evaluated the presence of DSM-5 psychiatric disorders. Future studies should also investigate potential association between clinical and motivational dimensions, such as negative symptoms, and education and work functioning that have been found in previous studies to be associated with daily-life functioning of 22q11.2DS individuals [16].

In conclusion, 22q11.2DS is a highly varied syndrome in terms of phenotype. In the present study, we focused on two pivotal aspects of functioning—education and employment. We presented variability in education between integration in mainstream classes in mainstream schools and special education schools. Similarly, variability was seen in employment ranging from employment in the open market to staying at home being too disabled to work. The fact that we found that cognitive abilities of children with 22q11.2DS predict school placement should urge health professionals to pay close attention to which school the child will attend, so that the school will be properly suited to his IQ to promote optimal development. In adulthood, adaptive functioning, more than cognitive abilities, was associated with employment. Thus, to improve outcomes of adults with 22q11.2DS, it may be helpful to create intervention techniques, beginning from adolescence, to facilitate a successful transition to adulthood in the area of employment, financial management and overall daily functioning.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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