Title

Cognitive Decline Preceding the Onset of Psychosis in Patients With 22q11.2 Deletion Syndrome

Journal

JAMA Psychiatry, 72(4)

ISSN

2168-622X

Authors

Vorstman, Jacob AS
Breetvelt, Elemi J
Duijff, Sasja N
et al.

Publication Date

2015-04-01

DOI

10.1001/jamapsychiatry.2014.2671

Peer reviewed

Original Investigation

Cognitive Decline Preceding the Onset of Psychosis in Patients With 22q11.2 Deletion Syndrome

Jacob A. S. Vorstman, MD, PhD; Elemi J. Breetvelt, MD, PhD; Sasja N. Duijff, PhD; Stephan Eliez, MD; Maude Schneider, MSc; Maria Jalbrzikowski, PhD; Marco Armando, MD, PhD; Stefano Vicari, MD, PhD; Vandana Shashi, MD; Stephen R. Hooper, PhD; Eva W. C. Chow, MD, MPH, FRCPC; Wai Lun Alan Fung, MD, ScD, FRCPC; Nancy J. Butcher, MSc; Donald A. Young, PhD, EdD; Donna M. McDonald-McGinn, MS, CGC; Annick Vogels, MD, PhD; Therese van Amelsvoort, MD, PhD; Doron Gothelf, MD; Ronnie Weinberger, MA; Abraham Weizman, MD; Petra W. J. Klaassen, MSc; Sanne Koops, MSc; Wendy R. Kates, PhD; Kevin M. Antshel, PhD; Tony J. Simon, PhD; Opal Y. Ousley, PhD; Ann Swillen, PhD; Raquel E. Gur, MD, PhD; Carrie E. Bearden, PhD; René S. Kahn, MD, PhD; Anne S. Bassett, MD, FRCPC; for the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome

IMPORTANCE Patients with 22q11.2 deletion syndrome (22q11DS) have an elevated (25%) risk of developing schizophrenia. Recent reports have suggested that a subgroup of children with 22q11DS display a substantial decline in cognitive abilities starting at a young age.

OBJECTIVE To determine whether early cognitive decline is associated with risk of psychotic disorder in 22q11DS.

DESIGN, SETTING, AND PARTICIPANTS Prospective longitudinal cohort study. As part of an international research consortium initiative, we used the largest data set of intelligence (IQ) measurements in patients with 22q11DS reported to date to investigate longitudinal IQ trajectories and the risk of subsequent psychotic illness. A total of 829 patients with a confirmed hemizygous 22q11.2 deletion, recruited through 12 international clinical research sites, were included. Both psychiatric assessments and longitudinal IQ measurements were available for a subset of 411 patients (388 with ≥1 assessment at age 8-24 years).

MAIN OUTCOMES AND MEASURES Diagnosis of a psychotic disorder, initial IQ, longitudinal IQ trajectory, and timing of the last psychiatric assessment with respect to the last IQ test.

RESULTS Among 411 patients with 22q11DS, 55 (13.4%) were diagnosed as having a psychotic disorder. The mean (SD) age at the most recent psychiatric assessment was 16.1 (6.2) years. The mean (SD) full-scale IQ at first cognitive assessment was lower in patients who developed a psychotic disorder (65.5 [12.0]) compared with those without a psychotic disorder (74.0 [14.0]). On average, children with 22q11DS showed a mild decline in IQ (full-scale IQ, 7.04 points) with increasing age, particularly in the domain of verbal IQ (9.02 points). In those who developed psychotic illness, this decline was significantly steeper ($P < .001$). Those with a negative deviation from the average cognitive trajectory observed in 22q11DS were at significantly increased risk for the development of a psychotic disorder (odds ratio = 2.49; 95% CI, 1.24-5.00; $P = .01$). The divergence of verbal IQ trajectories between those who subsequently developed a psychotic disorder and those who did not was distinguishable from age 11 years onward.

CONCLUSIONS AND RELEVANCE In 22q11DS, early cognitive decline is a robust indicator of the risk of developing a psychotic illness. These findings mirror those observed in idiopathic schizophrenia. The results provide further support for investigations of 22q11DS as a genetic model for elucidating neurobiological mechanisms underlying the development of psychosis.

JAMA Psychiatry. 2015;72(4):377-385. doi:10.1001/jamapsychiatry.2014.2671
Published online February 25, 2015.

Supplemental content at jamapsychiatry.com

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome members are listed at the end of this article.

Corresponding Author: Jacob A. S. Vorstman, MD, PhD, Department of Psychiatry, Brain Center Rudolf Magnus, A001.468, University Medical Center Utrecht, Heidelberglaan 100, 3485CX Utrecht, the Netherlands (j.a.s.vorstman@umcutrecht.nl).

Cognitive decline in schizophrenia is a fundamental component of the illness.[1] Importantly, this decline is evident years prior to the emergence of psychotic symptoms,[2-11] indicating that the onset of the disease process precedes the emergence of overt symptoms.[12] In clinical practice, psychosis is a necessary diagnostic criterion prompting initiation of treatment. The time lag between onset of the disease process and diagnosis of schizophrenia is a major challenge for research into early phases of the disorder. Given the prevalence of schizophrenia (approximately 1%), large samples are required to establish the association of early phenotypic changes with subsequent development of psychosis.

The 22q11.2 deletion syndrome (22q11DS) offers a valuable model to study risk mechanisms for schizophrenia. Approximately 25% of patients with 22q11DS develop schizophrenia,[13-16] making the associated hemizygous 1.2- to 3-megabase deletion on the long arm of chromosome 22[17,18] the strongest single genetic risk factor for the disorder.[19] The core phenotype of schizophrenia in 22q11DS, including the neurocognitive profile, is similar to that of schizophrenia in the general population.[20,21]

Patients with 22q11DS perform worse on neurocognitive tests such as verbal memory[21] and spatial working memory[22] after the onset of psychosis compared with those without psychosis. Psychotic disorder was associated with a deterioration of social and academic skills[23] as well as a deficit of approximately 8 IQ points[24] in cross-sectional studies, while previous longitudinal studies suggest that loss of cognitive skills, especially verbal IQ (VIQ), precedes the emergence of psychosis.[25-27] Such findings are consistent with observations of schizophrenia in the general population.[2-11,28] Although some decline relative to population norms, ie, developmental lag, is expected in children in the lower-IQ range,[29-31] a recent prospective longitudinal study found that about one-third of children with 22q11DS younger than 10 years display not only cognitive deficit relative to age norms but also an absolute decline in cognitive abilities.[32] Collectively, these initial studies suggest that in patients with 22q11DS, as in the general population, both early cognitive deficits as well as early cognitive decline could portend schizophrenia.

To our knowledge, this is the first multisite study on the developmental trajectory of intellectual abilities and psychosis in 22q11DS, reporting the largest longitudinal data set of patients with 22q11DS to date. We hypothesized that cognitive decline observed in children and adolescents with 22q11DS is associated with subsequent onset of psychotic illness.

Methods

Participants

A sample of 829 patients with 22q11DS was drawn from the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome, a collaboration of 22 research sites. Data include standardized cognitive and psychiatric assessments obtained from ongoing studies. Patients were selected based on availability of IQ measurements obtained with Wechsler intelligence scales (eg, Wechsler Preschool and Primary Scale of Intelligence, Wechsler Intelligence Scale for Children, Wechsler Abbreviated Scale of Intelligence, or Wechsler Adult Intelligence Scale)[33-36] and a structured diagnostic interview by a trained clinician.

Recruitment and Assessment

Patients were included in studies approved by the local institutional review board committees and with appropriate written informed consent. Presence of the 22q11.2 deletion was confirmed by established genetic methods. eTables 1, 2, and 3 in the Supplement present the sites, assessment methods, and demographic characteristics. The total data for 829 patients with 22q11DS generated cognitive development charts normative for 22q11DS; we use the term *22q11DS specific* throughout this article to distinguish these from norms derived from the general population. The association between IQ trajectory and psychotic disorder was examined in a subgroup of 388 patients with longitudinal data (**Figure 1**).

Diagnostic Categories

We defined psychotic disorder, herein termed *psychosis*, as any psychotic spectrum disorder, including schizophrenia (n = 20), schizoaffective disorder (n = 6), schizophreniform disorder (n = 3), brief psychotic disorder (n = 2), delusional disorder (n = 2), psychotic disorder not otherwise specified (n = 21), and type 1 bipolar disorder with psychotic features (n = 1). The relative timing of the most recent psychiatric assessment to the last cognitive measurement, pertinent to evaluating whether changes in IQ precede the onset of psychosis, is presented in **Table 1**.

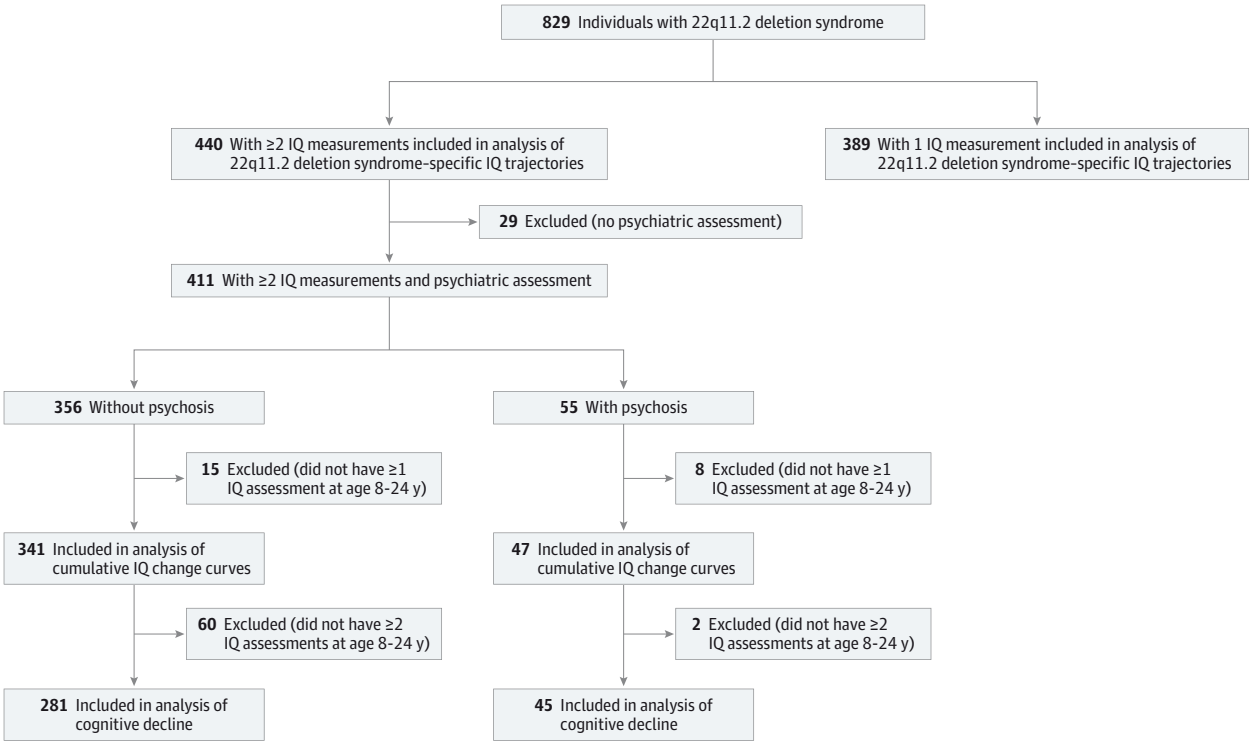
Statistical Analysis

Because of the limited number of IQ measures in patients younger than 8 years and older than 24 years, we restricted analyses to ages 8 to 24 years. We performed 3 analyses (Figure 1): (1) 22q11DS-specific IQ trajectory charts: IQ data from 829 patients with 22q11DS (389 with 1 assessment, 440 with ≥2 longitudinal assessments) yielded 1164 observations to construct 22q11DS-specific IQ trajectories; (2) cumulative IQ change curves: these analyses required data on psychiatric diagnosis and included a subset of 411 patients with 22q11DS (388 had ≥2 longitudinal IQ measurements, including one obtained between ages 8-24 years [341 without psychosis, 47 with psychosis at the most recent assessment]); and (3) calculation of effect size for cognitive decline: this subsample included 326 participants with at least 2 IQ measurements within the age range of 8 to 24 years (281 without psychosis, 45 with psychosis).

We used scaled IQ scores for all analyses. Because the development and stability of cognitive abilities in patients with 22q11DS deviate from those of the general population, we established a 22q11DS-specific chart for intellectual development in 22q11DS, similar to growth charts for patients with this[37] and other syndromes.[38] Individual IQ measurements were used to calculate percentiles for each age stratum. A 4-year-bin sliding window was applied to enhance accuracy of percentile estimation. Subsequently, percentile points were connected to generate percentile lines, which were smoothed using the Bézier curve procedure (R script; R Foundation). Smoothing percentile lines is a standard procedure in the development of normative charts.[39]

Change in IQ per year was calculated as the difference in IQ between 2 measurements divided by the number of interval years.

Figure 1. Flowchart of Selection Steps for Patients With 22q11.2 Deletion Syndrome



The IQ data from the 829 patients with 22q11.2 deletion syndrome (389 with 1 assessment, 440 with ≥2 longitudinal assessments) yielded 1164 observations at ages 8 to 24 years; the data set from these 1164 observations was used to generate the 22q11.2 deletion syndrome–specific IQ trajectories in eFigure 1 and eTable 1 in the Supplement. The data set from patients with at least 2 IQ measurements, with at least 1 of which performed at age 8 to 24 years, was used for the cumulative decline curves in Figure 2 and Figure 3. The data set from patients with at least 2 IQ measurements, with at least 2 of which performed at age 8 to 24 years, was used for calculation of the association of IQ decline with psychosis (eFigure 2 in the Supplement).

For each year (ages 8-24 years), the mean annualized IQ change was calculated (1695 calculated observations, on average 100 per year, with a minimum of 19 such observations at 24 years). The mean change in IQ per year of these observations (calculated separately for full-scale IQ [FSIQ], VIQ, and performance IQ [PIQ]) was used to construct the cumulative IQ trajectory curves.

The cumulative trajectories of IQ change over time are represented separately for those with and without psychosis. A bootstrap procedure evaluated the point at which the 95% confidence intervals of the 2 curves no longer overlapped, indicating a significantly different trajectory of the slopes. We performed a regression analysis to estimate the change in IQ as a function of age, containing linear and quadratic expressions of age as regressors, and allowing full interaction with diagnostic status. Thus, we tested whether the rate of linear change differed between patients with and without psychosis.

Next, we examined the strength of correlation between IQ decline and psychosis risk using the 22q11DS-specific chart of average IQ trajectory. We considered the difference in IQ percentile between 2 times as a categorical variable, comparing those with negative deviations from the original percentile vs those with increase or no change from the original percentile. Subsequently, the proportion of patients with psychosis was compared between those with and without IQ decline according to these categorical definitions. We used logistic regression analyses with psychosis as the primary outcome measure and IQ percentile decline as the dependent variable. Age at last assessment and sex were covariates. Next, IQ at the first measurement was added to the model as a continuous variable (and post hoc as a dichotomized variable using a median split). Finally, we examined the extent to which the timing of the most recent psychiatric assessment relative to the last cognitive measurement could have influenced the results. We performed a post hoc analysis with the time between the last IQ measurement and the last psychiatric assessment as a covariate in the logistic regression model.

Results

The mean (SD) age at the most recent psychiatric assessment in patients with at least 2 IQ measurements (n = 411; Figure 1) was 16.1 (6.2) years. The male to female ratio was 0.9 to 1, and 55 of 411 patients (13.4%) were diagnosed as having a psychotic disorder. Mean (SD) baseline IQ (ie, IQ at first cognitive assessment) was lower in this group (FSIQ, 65.5 [12.0]; VIQ, 67.5 [14.7]; PIQ, 65.0 [16.9]) compared with those without a psychotic disorder (FSIQ, 74.0 [14.0]; VIQ, 74.8 [18.6]; PIQ, 71.8 [16.6]). Overall, patients showed a decline in IQ over time, particularly in VIQ. The average total declines in cognitive abilities (ages 8-24 years) were 7.04 points in FSIQ, 9.02 points in VIQ, and 5.09 points in PIQ (**Figure 2**).

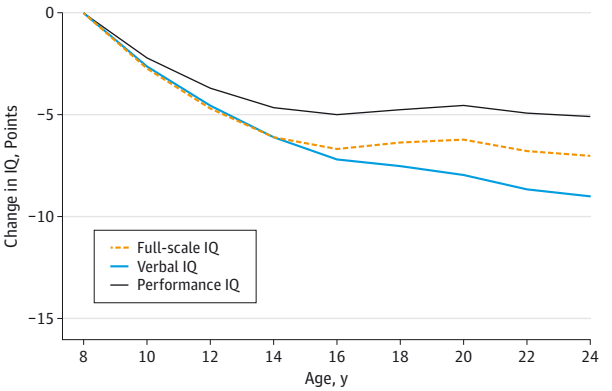
Table 1. Timing of Psychiatric Assessment Relative to Last Cognitive Assessment in 411 Patients With 22q11.2 Deletion Syndrome, and Diagnostic Classifications for the 55 Patients With Psychosis

Variable	Patients, No. (%)
Timing of psychiatric diagnosis[a]	
With psychosis (n = 55)	
Before last cognitive assessment	26 (47.3)
At same time as or after last cognitive assessment	29 (52.7)
Without psychosis (n = 356)	
Before last cognitive assessment	142 (39.9)
At same time as or after last cognitive assessment	214 (60.1)
All (n = 411)	
Before last cognitive assessment	168 (40.9)
At same time as or after last cognitive assessment	243 (59.1)
Diagnostic classification of psychotic disorders according to *DSM-IV* criteria (n = 55)[b]	
Schizophrenia	20 (35.7)
Schizophreniform disorder	3 (5.5)
Schizoaffective disorder	6 (10.9)
Delusional disorder	2 (3.6)
Brief psychotic disorder	2 (3.6)
Psychotic disorder not otherwise specified	21 (38.2)
Type 1 bipolar disorder, with prominent psychotic symptoms	1 (1.8)

[a] Psychiatric diagnosis before the last cognitive assessment indicates that the most recent psychiatric assessment was performed more than 3 months prior to the last cognitive assessment. Psychiatric diagnosis at the same time as or after the last cognitive assessment indicates that the most recent psychiatric assessment was within 3 months before or after the last cognitive assessment or at any time thereafter.

[b] In 1 patient, who had been previously assessed in direct interviews, the presence of psychosis was subsequently reported by parents by telephone.

Figure 2. Cumulative Plot of the Mean Annual IQ Decline per Age in 22q11.2 Deletion Syndrome



For each year, the average change in IQ is calculated and represented cumulatively for full-scale IQ, verbal IQ, and performance IQ for all 388 patients with 22q11.2 deletion syndrome for whom 2 or more IQ test results were available between ages 8 and 24 years. Note that this graph is not a longitudinal average trajectory. The average total declines in cognitive abilities (ages 8-24 years) were 7.04 points in full-scale IQ, 9.02 points in verbal IQ, and 5.09 points in performance IQ.

There was a significant difference in the slope of IQ trajectories; the psychosis group demonstrated a steeper decline than the nonpsychosis group (**Figure 3**). The difference was significant for FSIQ and both subscales ($P < .001$), but it was most pronounced for VIQ as illustrated by the larger effect size (partial η^2 of 0.07 for VIQ, 0.04 for FSIQ, and 0.01 for PIQ). The divergence of VIQ trajectories began early (Figure 3A), with the 95% confidence intervals of the VIQ trajectories for the 2 groups calculated with the bootstrap procedure not overlapping from age 11 years onward. Notably, the average age at onset of the first psychosis, estimated from the available clinical records, was 18.1 years (95% CI, 17.0-19.1), with the youngest age at onset being 12.7 years.

The mean (SD) age at psychiatric assessment differed between the nonpsychosis group (15.5 [5.8] years) and the psychosis group (20.1 [7.5] years) ($P < .001$). Importantly, the mean (SD) age at last cognitive assessment followed a similar pattern (16.3 [5.7] and 22.2 [9.3] years, respectively). To examine whether a change in IQ precedes the onset of psychosis, the last cognitive assessment should be performed before the psychiatric assessment. In our sample, both order and interval between the 2 assessments were variable. However, the proportion of patients with 22q11DS for whom their last psychiatric assessment preceded their last cognitive assessment was comparable between those with psychosis (47.3%) and those without psychosis (39.9%) ($P = .37$) (Table 1).

eFigure 1 in the Supplement presents 22q11DS-specific charts for the trajectory of intellectual development. Overall, there is a mild decrease in IQ between ages 8 and 24 years. From age 20 years onward, the number of available observations decreased substantially, limiting the accuracy of percentile trajectories.

Although all IQ slopes (FSIQ, VIQ, and PIQ) differed significantly between the two 22q11DS groups, the most pronounced deviation in trajectory between those with and those without psychosis was in VIQ. We therefore further examined this measure. Using the 22q11DS-specific chart, for each patient we assessed whether the results of the second VIQ measurement were consistent with or changed from the initial VIQ percentile. eFigure 2 in the Supplement shows a histogram of the distribution of deviations from VIQ percentile; the curve is skewed to the left and the subgroup with psychosis is overrepresented in the negative range. We therefore defined *cognitive decline* as a negative deviation from the trajectory expected in patients with 22q11DS.

Comparing those with and without a decline in VIQ, we found that patients with VIQ decline were more likely to develop a psychotic illness (18.2% vs 9.8%, respectively; odds ratio [OR] = 2.49; 95% CI, 1.24-5.00; $P = .01$) (**Table 2**). We then examined the extent to which low IQ at the first measurement could be a risk factor for psychosis. When added to the model, both the initial VIQ and the VIQ decline were significantly associated with an increased risk of psychosis (for initial IQ, OR = 0.97; 95% CI, 0.95-0.99; $P = .006$; for IQ decline: OR = 3.89; 95% CI, 1.73-8.75; $P = .001$). When initial IQ measurements alone were considered, only FSIQ at initial measurement was significantly associated with subsequent psychotic illness (OR = 0.96; 95% CI, 0.94-0.99; $P = .006$).

Given this observation, we examined initial IQ as a dichotomous variable in a post hoc analysis using a definition of potential clinical value. Regardless of subsequent decline, baseline FSIQ higher than 75 points was associated with lower risk for developing psychosis (OR = 2.73; 95% CI, 1.30-5.73; $P = .008$). We as-

sessed the possible influence of the interval between psychiatric and cognitive measurements, covarying for this interval in the logistic regression model. The findings were maintained, indicating that the difference in IQ trajectories between those with and those without psychosis could not wholly be attributed to variation of the interval between the last cognitive and psychiatric assessments (data not shown). Also, when restricting the analysis to the subgroup of patients in whom the psychiatric assessment either co-occurred or followed the last cognitive measurement (Table 1), the results were similar (difference in VIQ trajectories between those with and those without psychosis: OR = 2.56; 95% CI, 1.12-5.85; P = .03).

Discussion

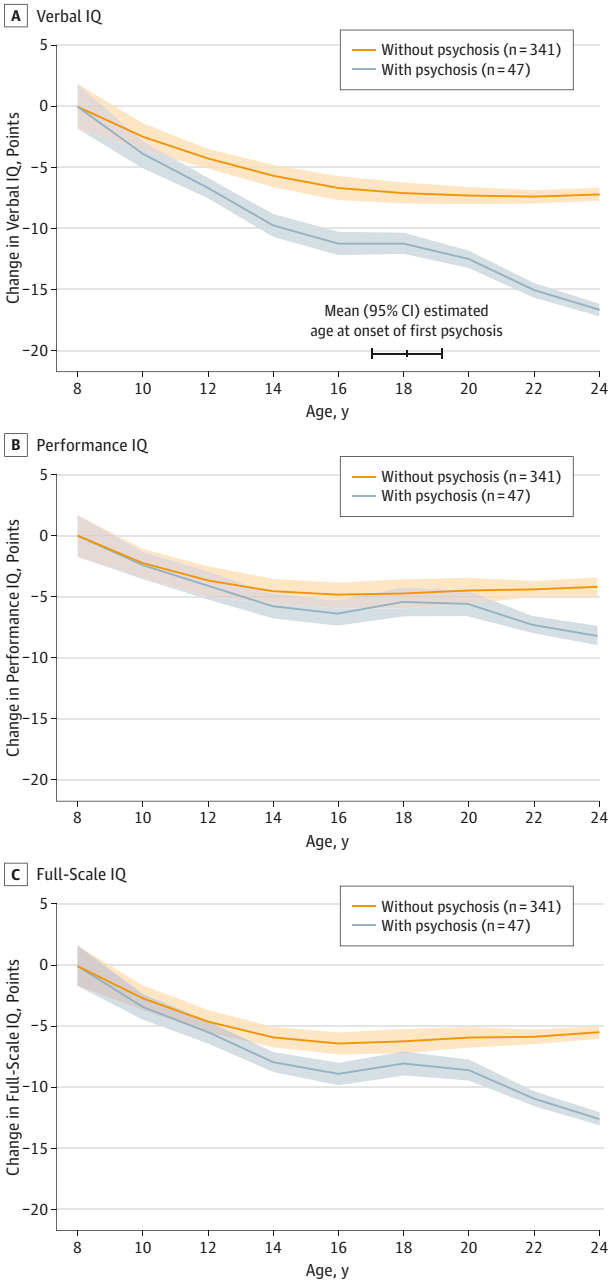
In the largest study, to our knowledge, conducted of the developmental trajectory of intellectual abilities in 22q11DS, we found that cognitive decline in patients with 22q11DS is greater in those who develop a psychotic disorder, and this decline appears to start as early as age 11 years. Those with a negative deviation from the average cognitive trajectory observed in 22q11DS had a 3-fold increased risk for the development of a psychotic disorder. This is further support that 22q11DS provides a unique opportunity to prospectively examine the pathophysiology of cognitive decline preceding the onset of psychosis.

Our results also suggest that cognitive decline could potentially become a useful marker in the clinical management of youths with 22q11DS. Several studies have reported potential markers for psychosis in 22q11DS, including changes in brain anatomy,[25,26,40-42] high plasma levels of the amino acid proline,[43-45] and genetic variation at the intact 22q11.2 allele.[46-48] However, measurement of these markers may be difficult to implement clinically owing to practical constraints and/or small effect sizes. Serial cognitive testing in 22q11DS is feasible in clinical practice[32] and the effect sizes reported herein may be clinically meaningful. Although independent replication and an understanding of the predictive values of cognitive change at the individual level are needed, our findings suggest the potential utility of implementing systematic surveillance of cognitive development in current clinical practice.

Our findings indicate that, regardless of subsequent decline, a relatively low initial IQ (<75 points) measured at or before the onset of adolescence is independently a risk factor for psychosis in 22q11DS. This finding is consistent with studies in the general population indicating that low IQ increases the risk for schizophrenia[8,49] and that this cognitive deficit is already apparent by age 13 years, long before the typical onset of psychosis.[50,51]

The study of cognition associated with schizophrenia (risk) encompasses different concepts,[52] including early developmental deficits that may remain stable over time and deficits that emerge during development. Decline observed in cognitive performance may be due to the phenomenon of developmental lag in which the cognitive growth is insufficient to keep up with the development observed in healthy peers. Alternatively, cognitive decline may also represent an absolute loss of previously acquired cognitive ability. The underlying mechanism of the cognitive decline observed in this study cannot be determined and could therefore be related to developmental

Figure 3. Cumulative Plots of the Mean Annual IQ Decline per Age in 22q11.2 Deletion Syndrome With Psychosis vs Without Psychosis



For each year, the average change in verbal IQ (A), performance IQ (B), and full-scale IQ (C) is calculated and represented cumulatively for both subgroups (patients with 22q11.2 deletion syndrome with vs without psychosis) in whom 2 or more IQ test results were available between ages 8 and 24 years (n = 388). Lines indicate means; shaded areas, 95% confidence intervals. Note that this graph is not a longitudinal average trajectory. This implies that the effect size of IQ decline between the 2 groups is not calculated by the absolute difference in IQ at any given age but by the difference in slope. In the patients diagnosed as having a psychotic disorder, the decline in IQ is steeper at most ages (P < .001), but it is most pronounced for verbal IQ as illustrated by the larger effect size (partial η^2 of 0.07 for verbal IQ, 0.04 for full-scale IQ, and 0.01 for performance IQ).

Table 2. Effect Size of IQ Decline With Respect to Diagnosis of a Psychotic Disorder in 22q11.2 Deletion Syndrome[a]

		VIQ		PIQ		FSIQ	
Model	Predictor	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
1	IQ decline	2.49 (1.24-5.00)	.01	1.14 (0.58-2.25)	.70	1.14 (0.58-2.24)	.70
2	IQ decline	3.89 (1.73-8.75)	.001	1.52 (0.71-3.26)	.29	1.86 (0.88-3.95)	.11
	Initial IQ, dimensional	0.97 (0.95-0.99)	.006	0.98 (0.96-1.00)	.09	0.96 (0.93-0.98)	.001
3	Initial IQ, dimensional	0.99 (0.97-1.01)	.29	0.99 (0.97-1.01)	.51	0.96 (0.94-0.99)	.006
4	Initial IQ <75 vs ≥75 points	1.95 (0.96-3.98)	.07	1.18 (0.58-2.40)	.65	2.73 (1.30-5.73)	.008

Abbreviations: FSIQ, full-scale IQ; OR, odds ratio; PIQ, performance IQ; VIQ, verbal IQ.

[a] Effect sizes (as ORs) and corresponding *P* values for logistic regression models with psychosis as the primary outcome and age at last IQ measurement and sex as covariates. In models 2 and 3, the initial IQ was examined as a continuous measure; therefore, the associated ORs reflect the effect size per IQ point change. In models 3 and 4, the age at initial IQ measurement was used as a covariate instead of age at last IQ measurement.

lag, absolute decline, or both. A previous study of patients with 22q11DS indicates that an absolute loss of cognitive abilities is likely to contribute to the observed decline.[32]

Low initial IQ and subsequent cognitive decline may be 2 independent phenomena, with the former reflecting suboptimal neurodevelopment leading to brain vulnerability to a broad range of psychopathology. Indeed, in the general population, low IQ increases the risk for many neuropsychiatric disorders.[49,53-55] Consistently, patients with 22q11DS have, on average, lower cognitive abilities compared with the general population and display a wide range of psychiatric disorders.[16,56,57] Early cognitive decline may reflect a distinct process in this genetic condition that may be specifically associated with the ensuing psychotic disorder. However, the nature of the association between psychosis and low IQ or decline in IQ cannot be inferred from our observations. It is possible that a deficit and/or decline in cognitive abilities renders the brain vulnerable to psychosis. Alternatively, both IQ changes and psychosis may be manifestations of the same mechanism. Findings from the Dunedin birth cohort[52] indicate that both a baseline cognitive deficit, measured at age 7 years, and a subsequent developmental lag in cognitive performance (particularly in domains indexing rapid information processing) between ages 7 and 13 years are associated with increased risk of idiopathic schizophrenia. Our results are largely consistent with these observations, although in contrast to findings in patients with 22q11DS,[32] no evidence for absolute cognitive deterioration was found in the Dunedin cohort.[52] Alternatively, it is possible that some patients with low initial IQ in our sample may have had IQ decline prior to the first cognitive measurement. Indeed, cognitive decline in 22q11DS has been observed between ages 5.5 and 9.5 years,[32] and approximately one-third of patients who show stable IQ after age 9.5 years have shown a decline in cognitive abilities between ages 7.5 and 9.5 years.[58] The apparent stabilization of the IQ trajectory between ages 16 and 20 years observed in our study (Figure 2 and Figure 3) may suggest that IQ decline before age 16 years is prodromal, while further decline after ages 18 to 20 years may be related to further cognitive deterioration associated with the emergence of psychosis itself and diminishing cognitive reserve.[59]

Several features make 22q11DS a unique model in which to study schizophrenia developmentally, particularly the trajectory from risk to disorder.[60] In 22q11DS, there are both a high risk for psychotic disorders (especially schizophrenia) caused by a specific genetic etiology and the frequent identification of this etiology very early in life, thus allowing follow-up across the life span. The occurrence of cognitive decline prior to the first psychotic episode,[1,6,61] observed in both 22q11DS and idiopathic schizophrenia, strongly suggests that psychosis is likely a late symptom of the disease. To increase our understanding of schizophrenia, more efforts should be directed toward elucidation of its early cognitive aspects.[12] The study of patients with 22q11DS provides a valuable contribution to this endeavor.

In particular, 1 or more genes within the deletion region or elsewhere in the genome may be involved in the etiology of both early cognitive decline and the ensuing expression of schizophrenia. The relative genetic homogeneity and the high risk of expression of these phenotypes in the 22q11DS population contrast with the general population, in which genetic contributions to schizophrenia are highly heterogeneous and risk is much lower. Therefore, studying 22q11DS as a genetic model for these phenotypes may facilitate the identification of contributing genes. Arguably, such genes may also be involved in the etiology of cognitive decline and schizophrenia in the general population.

The study has several limitations. A priori standardization of cognitive and psychiatric assessment methods across sites is lacking; however, in all patients the diagnosis of psychotic disorders was determined using the same (*DSM-IV*) classification criteria. Moreover, our cognitive data were restricted to those assessed with any of the Wechsler scales to optimize comparison over time and across sites. Timing of the psychiatric assessment in relation to last IQ testing is critical for discerning whether changes in IQ precede psychosis onset. The sequence was variable in our data set; however, in 59.1% of patients, the psychiatric assessment was performed either concurrently or after the last cognitive assessment. This proportion was not different between those with and those without psychosis. Importantly, the observed association between cognitive decline and psychosis did not change after inclusion of the interval between psychiatric and cognitive assessment as a covariate. Furthermore, the average estimated age at onset of psychosis was 18.1 years (95% CI, 17.0-19.1), much later than the age at which the divergence of VIQ appears (Figure 3A).

In this data set, the best estimate of psychosis onset was the time of the psychiatric assessment at which the diagnosis was made. The actual age at onset may differ as a function of the delay between the onset of symptoms and the psychiatric evaluation. However, given the awareness of the genetically mediated increased risk for psychotic disorders, patients with 22q11DS may tend to present for evaluation as soon as behavioral changes

emerge. Nevertheless, more accurate data on the actual age at onset of psychosis, and possibly the use of continuous measures of psychosis, will be valuable for future studies in this population. Another limitation is that the data are insufficient to estimate IQ changes beyond age 24 years, although there is evidence suggesting further cognitive decline in some adults with 22q11DS.[62] Ongoing data collection in several 22q11DS cohorts will provide such information. Finally, no information was available regarding socioeconomic status of the patients.

In many patients, the last psychiatric assessment was performed at a rather young age; therefore, some children currently not diagnosed as having a psychotic disorder may later develop psychosis. Ideally, the groups with and without psychosis should be matched for age. Restricting the sample to age-matched patients was not feasible owing to insufficient power. We therefore used age as a covariate in our analyses. Previous studies indicate that approximately 25% of patients with 22q11DS develop schizophrenia. In our study, only 13.4% had psychosis and thus a substantial proportion of patients currently classified as without psychosis may in reality be false-negatives. However, as a consequence, the IQ trajectory in the group without psychosis would be expected to show less decline than that observed. Thus, our data likely represent a conservative portrayal of the divergent IQ trajectories in patients with 22q11DS with and without psychosis.

Although our analyses were restricted to patients assessed with Wechsler scales, in some patients different versions were used. Those patients, particularly when a change occurred from WISC-III to WAIS, may demonstrate a change in IQ score resulting from different normative comparison groups between the 2 versions. Available evidence suggests that in comparison with the WISC, the WAIS tends to result in somewhat higher IQ scores.[63] Therefore, if the use of different Wechsler scales has influenced our results in any way, the changes from WISC to WAIS would be expected to mitigate the overall observed average decline in IQ in our patients with 22q11DS rather than to exaggerate it. Importantly, the proportion of patients in whom such a shift in test version occurred at follow-up was similar in the subgroup with psychosis (25.5%) and the subgroup without psychosis (24.4%), making this unlikely to explain the observed difference in IQ trajectories. Notwithstanding these limitations, this study is unprecedented in the large size of the cohort, the prospective design, and the restriction to 1 type of intelligence assessment.

Conclusions

Patients with 22q11DS who develop psychotic disorder show a significant cognitive decline, most pronounced in VIQ. This decline is significantly steeper than the intellectual decline over childhood and adolescence observed in patients with 22q11DS without psychosis. Importantly, the IQ trajectories in those with and without a psychotic disorder diverge at an early age, several years before the usual onset of psychosis in 22q11DS.[16,20,27] Our observations have potential ramifications for clinical management of patients with 22q11DS and for understanding the pathophysiology of schizophrenia, especially the importance of early cognitive decline preceding the first psychotic episode.

ARTICLE INFORMATION

Submitted for Publication: April 17, 2014; final revision received October 2, 2014; accepted October 20, 2014.

Published Online: February 25, 2015. doi:10.1001/jamapsychiatry.2014.2671.

Author Affiliations: Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, the Netherlands (Vorstman, Breetvelt, Duijff, Koops, Kahn); Office Médico-Pédagogique Research Unit, Department of Psychiatry, University of Geneva School of Medicine, Geneva, Switzerland (Eliez, Schneider); Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles (Jalbrzikowski, Bearden); Department of Psychology, University of California, Los Angeles (Jalbrzikowski, Bearden); Child Neuropsychiatry Unit, Department of Neuroscience, Bambino Gesù Children's Hospital, Rome, Italy (Armando, Vicari); Department of Pediatrics, Duke University Medical Center, Durham, North Carolina (Shashi); Department of Psychiatry, University of North Carolina School of Medicine, Chapel Hill (Hooper); Department of Allied Health Sciences, University of North Carolina School of Medicine, Chapel Hill (Hooper); Clinical Genetics Research Program, Centre for Addiction and Mental Health, Toronto, Ontario, Canada (Chow, Fung, Butcher, Young, Bassett); Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada (Chow, Fung, Young, Bassett); Dalglish Family Hearts and Minds Clinic for Adults With 22q11.2 Deletion Syndrome and Toronto General Research Institute, University Health Network, Toronto, Ontario, Canada (Fung, Bassett); Centre for Addiction and Mental Health, Toronto, Ontario, Canada (Fung, Bassett); Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada (Fung, Bassett); Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada (Butcher); Division of Human Genetics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania (McDonald-McGinn); Center for Human Genetics, KU Leuven, Leuven, Belgium (Vogels, Swillen); Department of Psychiatry and Psychology, Maastricht University, Maastricht, the Netherlands (van Amelsvoort); Behavioral Neurogenetics Center, The Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, Israel (Gothelf, Weinberger); Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel (Gothelf, Weinberger, Weizman); Felsenstein Medical Research Center, Petah Tikva, Israel (Weizman); Geha Mental Health Center, Petah Tikva, Israel (Weizman); Department of Pediatric Psychology, Wilhelmina Children's Hospital, University Medical Center, Utrecht, the Netherlands (Klaassen); Department of Psychiatry and Behavioral Sciences, Upstate Medical University, State University of New York, Syracuse (Kates, Antshel); Department of Psychology, Syracuse University, Syracuse, New York (Antshel); MIND (Medical Investigation of Neurodevelopmental Disorders) Institute and Department of Psychiatry and Behavioral Sciences, University of California, Davis (Simon); Emory Autism Center, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia (Ousley); Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia (Gur).

Author Contributions: Dr Vorstman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Vorstman and Breetvelt contributed equally to this work.
Study concept and design: Vorstman, Duijff, McDonald-McGinn, Antshel, Ousley, Swillen, Gur, Bearden, Kahn, Bassett.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Vorstman, Breetvelt, McDonald-McGinn, Weinberger, Weizman, Koops, Antshel, Swillen, Gur, Bearden, Bassett.
Critical revision of the manuscript for important intellectual content: Vorstman, Duijff, Eliez, Schneider, Jalbrzikowski, Armando, Vicari, Shashi, Hooper, Chow, Fung, Butcher, Young, McDonald-McGinn, Vogels, van Amelsvoort, Gothelf, Weizman, Klaassen, Kates, Antshel, Simon, Ousley, Swillen, Gur, Bearden, Kahn, Bassett.
Statistical analysis: Vorstman, Breetvelt, Fung, Antshel.
Obtained funding: Vorstman, Eliez, Hooper, McDonald-McGinn, Antshel, Simon, Ousley, Gur, Bearden, Bassett.
Administrative, technical, or material support: Eliez,

Jalbrzikowski, Chow, Butcher, Young, McDonald-McGinn, Gothelf, Weinberger, Koops, Simon, Ousley, Gur, Kahn, Bassett.
Study supervision: Armando, Vicari, Young, McDonald-McGinn, Vogels, Weizman, Swillen, Bearden, Kahn, Bassett.

Conflict of Interest Disclosures: Dr Hooper reported providing consultation to Novartis. Dr Ousley reported being a collaborator in a Biomarin Pharmaceutical study. No other disclosures were reported.

Funding/Support: This study was supported by the National Institutes of Mental Health International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome; grants PP00B_102864 and 32473B_121996 from the Swiss National Fund (Dr Eliez); grant 51AU40_125759 from the National Center of Competence in Research–Synapsy, financed by the Swiss National Science Foundation (Dr Eliez); grants MOP-97800, MOP-89066, and MOP-74631 from the Canadian Institutes of Health Research (Drs Bassett and Chow); the Ontario Mental Health Foundation (Dr Chow); the Canada Research Chair in Schizophrenia Genetics and Genomic Disorders and the Dalglish Chair in 22q11.2 Deletion Syndrome (Dr Bassett); grant 2315/1 from the Baily Thomas Charitable Trust (Marianne B. M. van den Bree, PhD, of the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome); grant 912-1234 from the Waterloo Foundation (Dr van den Bree); the Wellcome Trust Institutional Strategic Support Fund (Dr van den Bree); grants RP/2004/30 and RP/2008/169 from Ireland's Health Research Board (Kieran C. Murphy, MD, PhD, of the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome); grant 1206/188 from the Health Foundation (Dr K. C. Murphy); grants MH-064824 and MH-065481 (Dr Kates), MH-087626 (Dr Gur), MH-087636 (Ms McDonald-McGinn and Elaine H. Zackai, MD, of the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome), MH-078015 and MH-091314 (Dr Shashi), R01 MH-085953 and R01 HD065280 (Dr Bearden), and 1U01MH101724-01 (Drs van den Bree and K. C. Murphy and Declan Murphy, MD, and Celso Arango, MD, PhD, of the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome) from the National Institutes of Mental Health; grants HD-070454 (Ms McDonald-McGinn and Dr Zackai), P50 HD-055784 (CART pilot project grant) (Dr Bearden), and R01 HD-042974 (Dr Simon) from the National Institute of Child Health and Human Development; the Young Investigator Award from the Brain and Behavior Research Foundation (Drs Vorstman, van Amelsvoort, and Armando); the Brain and Behavior Research Foundation (Dr Ousley); the State University of New York Hendricks Fund (Dr Antshel); Basil O'Connor Starter Scholar Research Award 5-FY06-590 from the March of Dimes (Dr Gothelf); grant 2011378 from the Binational Science Foundation (Dr Gothelf); the Gazit-Globe Award (Tamar Green, MD, of the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome); the Dutch Brain Foundation (Dr van Amelsvoort); the Robert W. Woodruff Fund (Dr Ousley); the Simons Foundation (Dr Ousley); a postdoctoral fellowship from the Hunter Medical Research Institute (Linda E. Campbell, PhD, of the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome); and Australian Training Fellowship 455614 from the National Health and Medical Research Council of Australia (Dr Simon).

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: The International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome members include Beverly S. Emanuel, PhD, Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia; Elaine H. Zackai, MD, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; Leila Kushan, MSc, Semel Institute for Neuroscience and Human Behavior, Los Angeles, California; Wanda Fremont, MD, Upstate Medical University, State University of New York, Syracuse; Kelly Schoch, MS, Duke University Medical Center, Durham, North Carolina; Joel Stoddard, MD, MIND (Medical Investigation of Neurodevelopmental Disorders) Institute and Department of Psychiatry and Behavioral Sciences, University of California, Davis; Joseph Cubells, MD, PhD, Emory Autism Center, Emory University School of Medicine, Atlanta, Georgia; Fiona Fu, Clinical Genetics Research Program, Centre for Addiction and Mental Health, University of Toronto, Toronto, Ontario, Canada; Linda E. Campbell, PhD, School of Psychology, University of Newcastle, Ourimbah, Australia, and Priority Research Centre for Translational Neuroscience and Mental Health, University of Newcastle, Newcastle, Australia; Rosemarie Fritsch, MD, Facultad de Medicina, Universidad de Chile, Santiago, Chile; Elfi Vergaelen, MD, Center for Human Genetics, KU Leuven, Leuven, Belgium; Marjolein Neeleman, MD, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, the Netherlands; Erik Boot, MD, PhD, Academic Medical Centre, Amsterdam, the Netherlands; Martin Debbané, PhD, Office Médico-Pédagogique Research Unit, Department of Psychiatry, University of Geneva School of Medicine, Geneva, Switzerland; Nicole Philip, MD, Aix-Marseille Université, INSERM, Unité Mixte de Recherche S910, Génétique Médicale et Génomique Fonctionnelle and Hôpital de la Timone, Assistance Publique, Hôpitaux de Marseille, Marseille, France; Tamar Green, MD, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; Marianne B. M. van den Bree, PhD, MRC Centre for Neuropsychiatric Genetics and Genomics, Institute of Psychological Medicine and Clinical Neurosciences, Cardiff University, Cardiff, Wales; Declan Murphy, MD, Sackler Institute for Translational Neurodevelopment and Department of Forensic and Neurodevelopmental Sciences, King's College London, Institute of Psychiatry, London, England; Jaume Morey Canyelles, MD, PhD, Balearic Institute of Child and Adolescent Mental Health, Son Espases University Hospital, Mallorca, Spain; Celso Arango, MD, PhD, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, School of Medicine, Universidad Complutense, Centro de Investigación Biomédica en Red en el Área de Salud Mental, Madrid, Spain; Kieran C. Murphy, MD, PhD, School of Medicine, Royal College of Surgeons in Ireland, Dublin, Ireland; and Maria Pontillo, PhD, Bambino Gesù Children's Hospital, Rome, Italy

REFERENCES

1. Kraepelin E. *Dementia Praecox and Paraphrenia*. Barclay RM, trans. Robertson GM, ed. Chicago, IL: Chicago Medical Book Co; 1919.

2. Reichenberg A, Weiser M, Rapp MA, et al. Elaboration on premorbid intellectual performance in schizophrenia: premorbid intellectual decline and risk for schizophrenia. *Arch Gen Psychiatry*. 2005; 62(12):1297-1304.

3. Cannon TD, Bearden CE, Hollister JM, Rosso IM, Sanchez LE, Hadley T. Childhood cognitive functioning in schizophrenia patients and their unaffected siblings: a prospective cohort study. *Schizophr Bull*. 2000;26(2):379-393.

4. Bearden CE, Rosso IM, Hollister JM, Sanchez LE, Hadley T, Cannon TD. A prospective cohort study of childhood behavioral deviance and language abnormalities as predictors of adult schizophrenia. *Schizophr Bull*. 2000;26(2):395-410.

5. Cannon M, Caspi A, Moffitt TE, et al. Evidence for early-childhood, pan-developmental impairment specific to schizophreniform disorder: results from a longitudinal birth cohort. *Arch Gen Psychiatry*. 2002;59(5):449-456.

6. Fuller R, Nopoulos P, Arndt S, O'Leary D, Ho BC, Andreasen NC. Longitudinal assessment of premorbid cognitive functioning in patients with schizophrenia through examination of standardized scholastic test performance. *Am J Psychiatry*. 2002;159(7):1183-1189.

7. Rabinowitz J, De Smedt G, Harvey PD, Davidson M. Relationship between premorbid functioning and symptom severity as assessed at first episode of psychosis. *Am J Psychiatry*. 2002;159(12):2021-2026.

8. Woodberry KA, Giuliano AJ, Seidman LJ. Premorbid IQ in schizophrenia: a meta-analytic review. *Am J Psychiatry*. 2008;165(5):579-587.

9. Keefe RS, Perkins DO, Gu H, Zipursky RB, Christensen BK, Lieberman JA. A longitudinal study of neurocognitive function in individuals at-risk for psychosis. *Schizophr Res*. 2006;88(1-3):26-35.

10. Cosway R, Byrne M, Clafferty R, et al. Neuropsychological change in young people at high risk for schizophrenia: results from the first two neuropsychological assessments of the Edinburgh High Risk Study. *Psychol Med*. 2000;30(5):1111-1121.

11. Meier MH, Caspi A, Reichenberg A, et al. Neuropsychological decline in schizophrenia from the premorbid to the postonset period: evidence from a population-representative longitudinal study. *Am J Psychiatry*. 2014;171(1):91-101.

12. Kahn RS, Keefe RS. Schizophrenia is a cognitive illness: time for a change in focus. *JAMA Psychiatry*. 2013;70(10):1107-1112.

13. Murphy KC, Jones LA, Owen MJ. High rates of schizophrenia in adults with velo-cardio-facial syndrome. *Arch Gen Psychiatry*. 1999;56(10):940-945.

14. Shprintzen RJ, Goldberg R, Golding-Kushner KJ, Marion RW. Late-onset psychosis in the velo-cardio-facial syndrome. *Am J Med Genet*. 1992;42(1):141-142.

15. Vorstman JA, Morcus ME, Duijff SN, et al. The 22q11.2 deletion in children: high rate of autistic disorders and early onset of psychotic symptoms. *J Am Acad Child Adolesc Psychiatry*. 2006;45(9): 1104-1113.

16. Schneider M, Debbané M, Bassett AS, et al; International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: results from the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. *Am J Psychiatry*. 2014;171(6):627-639.

17. Edelmann L, Pandita RK, Spiteri E, et al. A common molecular basis for rearrangement disorders on chromosome 22q11. *Hum Mol Genet*. 1999;8(7):1157-1167.

18. Shaikh TH, Kurahashi H, Saitta SC, et al. Chromosome 22-specific low copy repeats and the 22q11.2 deletion syndrome: genomic organization and deletion endpoint analysis. *Hum Mol Genet*. 2000;9(4):489-501.

19. Karayiorgou M, Simon TJ, Gogos JA. 22q11.2 microdeletions: linking DNA structural variation to brain dysfunction and schizophrenia. *Nat Rev Neurosci*. 2010;11(6):402-416.

20. Bassett AS, Chow EW, AbdelMalik P, Gheorghiu M, Husted J, Weksberg R. The schizophrenia phenotype in 22q11 deletion syndrome. *Am J Psychiatry*. 2003;160(9):1580-1586.

21. Chow EW, Watson M, Young DA, Bassett AS. Neurocognitive profile in 22q11 deletion syndrome and schizophrenia. *Schizophr Res*. 2006;87(1-3):270-278.

22. van Amelsvoort T, Henry J, Morris R, et al. Cognitive deficits associated with schizophrenia in velo-cardio-facial syndrome. *Schizophr Res*. 2004;70(2-3):223-232.

23. Yuen T, Chow EW, Silversides CK, Bassett AS. Premorbid adjustment and schizophrenia in individuals with 22q11.2 deletion syndrome. *Schizophr Res*. 2013;151(1-3):221-225.

24. Green T, Gothelf D, Glaser B, et al. Psychiatric disorders and intellectual functioning throughout development in velocardiofacial (22q11.2 deletion) syndrome. *J Am Acad Child Adolesc Psychiatry*. 2009;48(11):1060-1068.

25. Gothelf D, Eliez S, Thompson T, et al. COMT genotype predicts longitudinal cognitive decline and psychosis in 22q11.2 deletion syndrome. *Nat Neurosci*. 2005;8(11):1500-1502.

26. Kates WR, Antshel KM, Faraone SV, et al. Neuroanatomic predictors to prodromal psychosis in velocardiofacial syndrome (22q11.2 deletion syndrome): a longitudinal study. *Biol Psychiatry*. 2011;69(10):945-952.

27. Gothelf D, Schneider M, Green T, et al. Risk factors and the evolution of psychosis in 22q11.2 deletion syndrome: a longitudinal 2-site study. *J Am Acad Child Adolesc Psychiatry*. 2013;52(11):1192-1203.e3.

28. Lane EA, Albee GW. On childhood intellectual decline of adult schizophrenics: a reassessment of an earlier study. *J Abnorm Psychol*. 1968;73(2):174-177.

29. Bos K. Relationship between cognitive development, decoding skill, and reading comprehension in learning-disabled Dutch children. In: Aaron PG, Joshi RM, eds. *Reading and Writing Disorders in Different Orthographic Systems*. Vol 52. Houten, the Netherlands: Springer Netherlands; 1989:75-86.

30. Share DL, Silva PA. Language deficits and specific reading retardation: cause or effect? *Br J Disord Commun*. 1987;22(3):219-226.

31. Shaywitz BA, Holford TR, Holahan JM, et al. A Matthew effect for IQ but not for reading: results from a longitudinal study. *Read Res Q*. 1995;30(4):894-906.

32. Duijff SN, Klaassen PW, de Veye HF, Beemer FA, Sinnema G, Vorstman JA. Cognitive development in children with 22q11.2 deletion syndrome. *Br J Psychiatry*. 2012;200(6):462-468.

33. Wechsler D. *Wechsler Intelligence Scale for Children*. 3rd ed. San Antonio, TX: Psychological Corp; 1991.

34. Wechsler D. *Wechsler Preschool and Primary Scale of Intelligence*. 3rd ed. San Antonio, TX: Psychological Corp; 2002.

35. Wechsler D. *Wechsler Intelligence Scale for Children*. 4th ed. San Antonio, TX: Psychological Corp; 2003.

36. Wechsler D. *Wechsler Adult Intelligence Scale*. 4th ed. San Antonio, TX: Psychological Corp; 2008.

37. Habel A, McGinn MJ II, Zackai EH, Unanue N, McDonald-McGinn DM. Syndrome-specific growth charts for 22q11.2 deletion syndrome in Caucasian children. *Am J Med Genet A*. 2012;158A(11):2665-2671.

38. Myrelid A, Gustafsson J, Ollars B, Annerén G. Growth charts for Down's syndrome from birth to 18 years of age. *Arch Dis Child*. 2002;87(2):97-103.

39. van Buuren S, Fredriks M. Worm plot: a simple diagnostic device for modelling growth reference curves. *Stat Med*. 2001;20(8):1259-1277.

40. Schaer M, Debbané M, Bach Cuadra M, et al. Deviant trajectories of cortical maturation in 22q11.2 deletion syndrome (22q11DS): a cross-sectional and longitudinal study. *Schizophr Res*. 2009;115(2-3):182-190.

41. Chow EW, Ho A, Wei C, Voormolen EH, Crawley AP, Bassett AS. Association of schizophrenia in 22q11.2 deletion syndrome and gray matter volumetric deficits in the superior temporal gyrus. *Am J Psychiatry*. 2011;168(5):522-529.

42. da Silva Alves F, Schmitz N, Bloemen O, et al. White matter abnormalities in adults with 22q11 deletion syndrome with and without schizophrenia. *Schizophr Res*. 2011;132(1):75-83.

43. Raux G, Bumsel E, Hecketsweiler B, et al. Involvement of hyperprolinemia in cognitive and psychiatric features of the 22q11 deletion syndrome. *Hum Mol Genet*. 2007;16(1):83-91.

44. Vorstman JA, Turetsky BI, Sijmens-Morcus ME, et al. Proline affects brain function in 22q11DS children with the low activity COMT 158 allele. *Neuropsychopharmacology*. 2009;34(3):739-746.

45. Magnée MJ, Lamme VA, de Sain-van der Velden MG, Vorstman JA, Kemner C. Proline and COMT status affect visual connectivity in children with 22q11.2 deletion syndrome. *PLoS One*. 2011;6(10):e25882.

46. Williams NM, Glaser B, Norton N, et al. Strong evidence that *GNB1L* is associated with schizophrenia. *Hum Mol Genet*. 2008;17(4):555-566.

47. Vorstman JA, Chow EW, Ophoff RA, et al. Association of the PIK4CA schizophrenia-susceptibility gene in adults with the 22q11.2 deletion syndrome. *Am J Med Genet B Neuropsychiatr Genet*. 2009;150B(3):430-433.

48. Gothelf D, Feinstein C, Thompson T, et al. Risk factors for the emergence of psychotic disorders in adolescents with 22q11.2 deletion syndrome. *Am J Psychiatry*. 2007;164(4):663-669.

49. Zammit S, Allebeck P, David AS, et al. A longitudinal study of premorbid IQ score and risk of developing schizophrenia, bipolar disorder, severe depression, and other nonaffective psychoses. *Arch Gen Psychiatry*. 2004;61(4):354-360.

50. Dickson H, Laurens KR, Cullen AE, Hodgins S. Meta-analyses of cognitive and motor function in youth aged 16 years and younger who subsequently develop schizophrenia. *Psychol Med*. 2012;42(4):743-755.

51. van Oel CJ, Sitskoorn MM, Cremer MP, Kahn RS. School performance as a premorbid marker for schizophrenia: a twin study. *Schizophr Bull*. 2002;28(3):401-414.

52. Reichenberg A, Caspi A, Harrington H, et al. Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: a 30-year study. *Am J Psychiatry*. 2010;167(2):160-169.

53. Dekker MC, Koot HM, van der Ende J, Verhulst FC. Emotional and behavioral problems in children and adolescents with and without intellectual disability. *J Child Psychol Psychiatry*. 2002;43(8):1087-1098.

54. Koenen KC, Moffitt TE, Roberts AL, et al. Childhood IQ and adult mental disorders: a test of the cognitive reserve hypothesis. *Am J Psychiatry*. 2009;166(1):50-57.

55. Gale CR, Deary IJ, Boyle SH, Barefoot J, Mortensen LH, Batty GD. Cognitive ability in early adulthood and risk of 5 specific psychiatric disorders in middle age: the Vietnam experience study. *Arch Gen Psychiatry*. 2008;65(12):1410-1418.

56. Baker K, Vorstman JA. Is there a core neuropsychiatric phenotype in 22q11.2 deletion syndrome? *Curr Opin Neurol*. 2012;25(2):131-137.

57. Tang SX, Yi JJ, Calkins ME, et al. Psychiatric disorders in 22q11.2 deletion syndrome are prevalent but undertreated. *Psychol Med*. 2014;44(6):1267-1277.

58. Duijff SN, Klaassen PW, Swanenburg de Veye HF, Beemer FA, Sinnema G, Vorstman JA. Cognitive and behavioral trajectories in 22q11DS from childhood into adolescence: a prospective 6-year follow-up study. *Res Dev Disabil*. 2013;34(9):2937-2945.

59. Hedman AM, van Haren NE, van Baal CG, Kahn RS, Hulshoff Pol HE. IQ change over time in schizophrenia and healthy individuals: a meta-analysis. *Schizophr Res*. 2013;146(1-3):201-208.

60. Insel TR. Rethinking schizophrenia. *Nature*. 2010;468(7321):187-193.

61. Pukrop R, Ruhrmann S, Schultze-Lutter F, Bechdolf A, Brockhaus-Dumke A, Klosterkötter J. Neurocognitive indicators for a conversion to psychosis: comparison of patients in a potentially initial prodromal state who did or did not convert to a psychosis. *Schizophr Res*. 2007;92(1-3):116-125.

62. Evers LJ, van Amelsvoort TA, Candel MJ, Boer H, Engelen JJ, Curfs LM. Psychopathology in adults with 22q11 deletion syndrome and moderate and severe intellectual disability. *J Intellect Disabil Res*. 2014;58(10):915-925.

63. Kaufman AS, Lichtenberger OL. *Assessing Adolescent and Adult Intelligence*. 3rd ed. Hoboken, NJ: John Wiley & Sons; 2006.