

## Original Investigation

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

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**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  $\geq 1$  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.

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Cognitive decline in schizophrenia is a fundamental component of the illness.<sup>1</sup> Importantly, this decline is evident years prior to the emergence of psychotic symptoms,<sup>2-11</sup> indicating that the onset of the disease process precedes the emergence of overt symptoms.<sup>12</sup> 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,<sup>13-16</sup> making the associated hemizygous 1.2- to 3-megabase deletion on the long arm of chromosome 22<sup>17,18</sup> the strongest single genetic risk factor for the disorder.<sup>19</sup> The core phenotype of schizophrenia in 22q11DS, including the neurocognitive profile, is similar to that of schizophrenia in the general population.<sup>20,21</sup>

Patients with 22q11DS perform worse on neurocognitive tests such as verbal memory<sup>21</sup> and spatial working memory<sup>22</sup> after the onset of psychosis compared with those without psychosis. Psychotic disorder was associated with a deterioration of social and academic skills<sup>23</sup> as well as a deficit of approximately 8 IQ points<sup>24</sup> in cross-sectional studies, while previous longitudinal studies suggest that loss of cognitive skills, especially verbal IQ (VIQ), precedes the emergence of psychosis.<sup>25-27</sup> Such findings are consistent with observations of schizophrenia in the general population.<sup>2-11,28</sup> Although some decline relative to population norms, ie, developmental lag, is expected in children in the lower-IQ range,<sup>29-31</sup> 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.<sup>32</sup> 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 Intel-

ligence Scale)<sup>33-36</sup> 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.

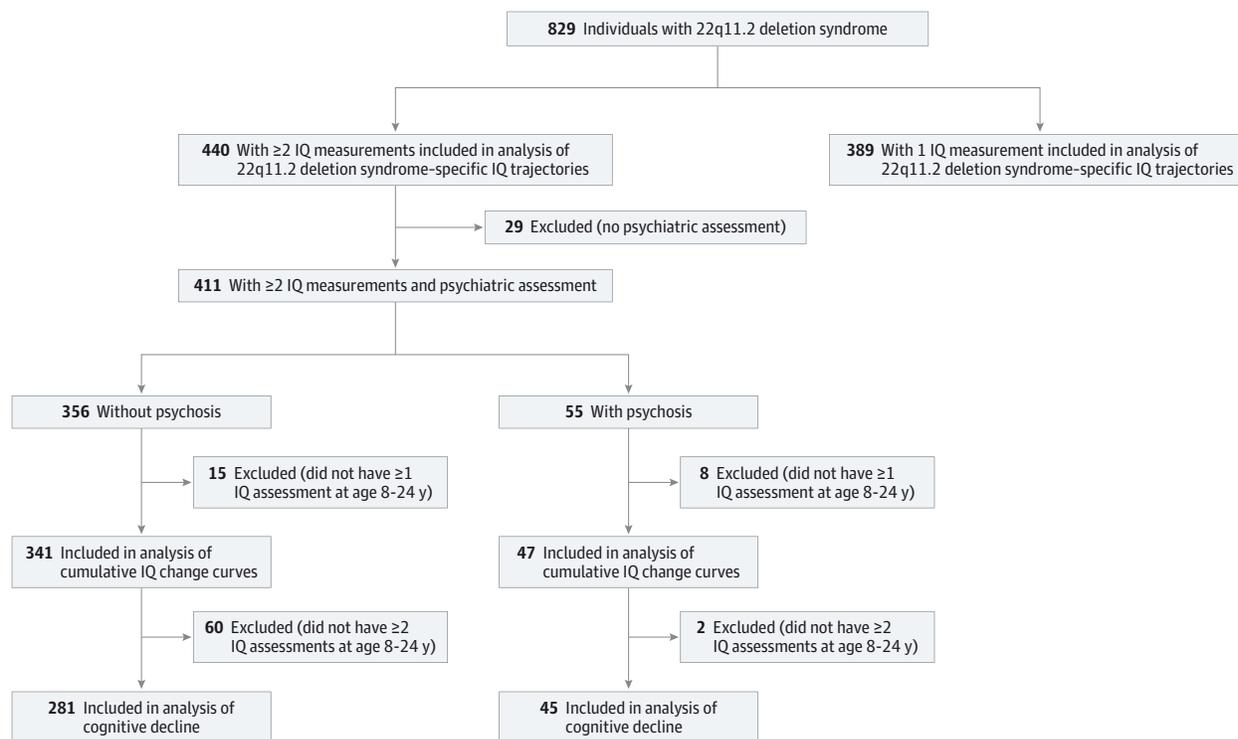
### Statistical Analysis

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  $\geq 2$  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  $\geq 2$  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<sup>37</sup> and other syndromes.<sup>38</sup> 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.<sup>39</sup>

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  $\geq 2$  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 <sup>a</sup>	
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) <sup>b</sup>	
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)

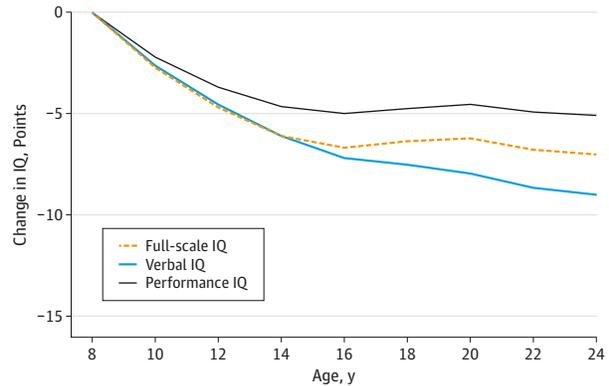
<sup>a</sup> Psychiatric diagnosis before the last cognitive assessment indicates that the most recent psychiatric assessment was performed more than 3 months prior to the last cognitive assessment. Psychiatric diagnosis at the same time as or after the last cognitive assessment indicates that the most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

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

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  $\eta^2$  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).

**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.

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-

essed 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

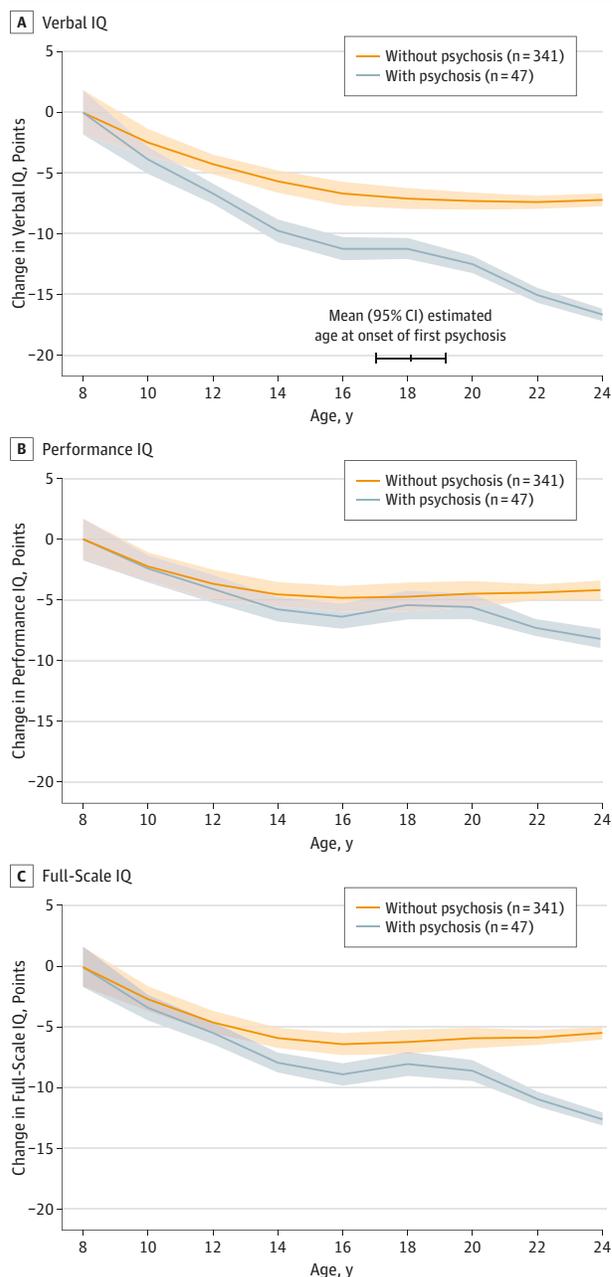
In the largest study, to our knowledge, conducted of the developmental trajectory of intellectual abilities in 22q11DS, we found that cognitive decline in patients with 22q11DS is greater in those who develop a psychotic disorder, and this decline appears to start as early as age 11 years. Those with 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,<sup>25,26,40-42</sup> high plasma levels of the amino acid proline,<sup>43-45</sup> and genetic variation at the intact 22q11.2 allele.<sup>46-48</sup> 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<sup>32</sup> 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<sup>8,49</sup> and that this cognitive deficit is already apparent by age 13 years, long before the typical onset of psychosis.<sup>50,51</sup>

The study of cognition associated with schizophrenia (risk encompasses different concepts,<sup>52</sup> 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 mecha-

**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  $\eta^2$  of 0.07 for verbal IQ, 0.04 for full-scale IQ, and 0.01 for performance IQ).

nism of the cognitive decline observed in this study cannot be determined and could therefore be related to developmental

Table 2. Effect Size of IQ Decline With Respect to Diagnosis of a Psychotic Disorder in 22q11.2 Deletion Syndrome<sup>a</sup>

Model	Predictor	VIQ		PIQ		FSIQ	
		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.

<sup>a</sup> 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.<sup>32</sup>

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.<sup>49,53-55</sup> Consistently, patients with 22q11DS have, on average, lower cognitive abilities compared with the general population and display a wide range of psychiatric disorders.<sup>16,56,57</sup> 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<sup>52</sup> 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,<sup>32</sup> no evidence for absolute cognitive deterioration was found in the Dunedin cohort.<sup>52</sup> 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,<sup>32</sup> 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.<sup>58</sup> 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.<sup>59</sup>

Several features make 22q11DS a unique model in which to study schizophrenia developmentally, particularly the trajectory from risk to disorder.<sup>60</sup> 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 eti-

ology very early in life, thus allowing follow-up across the life span. The occurrence of cognitive decline prior to the first psychotic episode,<sup>1,6,61</sup> 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.<sup>12</sup> 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.<sup>62</sup> 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.<sup>63</sup> 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.<sup>16,20,27</sup> 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

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