Subthreshold Psychosis in 22q11.2 Deletion Syndrome: Multi-site Naturalistic Study

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Abstract

Nearly one-third of individuals with 22q11.2 deletion syndrome (22q11.2DS) develop a psychotic disorder during life, most of them by early adulthood. Importantly, a full-blown psychotic episode is usually preceded by subthreshold symptoms. In the current study, 760 participants (ages 6–55 years) with a confirmed hemizygous 22q11.2 microdeletion have been recruited through 10 medical sites worldwide, as part of an international research consortium. Of them, 692 were non-psychotic and with complete measurement data. Subthreshold psychotic symptoms were assessed using the Structured Interview for Prodromal Syndromes (SIPS). Nearly one-third of participants met criteria for positive subthreshold psychotic symptoms (32.8%), less than 1% qualified for acute positive subthreshold symptoms, and almost a quarter met criteria for negative/disorganized subthreshold symptoms (21.7%). Adolescents and young adults (13–25 years) showed the highest rates of subthreshold psychotic symptoms. Additionally, higher rates of anxiety disorders and attention deficit/hyperactivity disorder (ADHD) were found among the study participants with subthreshold psychotic symptoms compared to those without. Full-scale IQ, verbal IQ, and global functioning (GAF) scores were negatively associated with participants’ subthreshold psychotic symptoms. This study represents the most comprehensive analysis reported to date on subthreshold psychosis in 22q11.2DS. Novel findings include age-related changes in subthreshold psychotic symptoms and evidence that cognitive deficits are associated with subthreshold psychosis in this population. Future studies should longitudinally follow these symptoms to detect whether and how early identification and treatment of these manifestations can improve long-term outcomes in those that eventually develop a psychotic disorder.
Introduction

22q11.2 deletion syndrome (22q11.2DS) is a genetic disorder that occurs in about 1 in 4,000 live births.\(^1\) Psychiatric comorbidities are highly prevalent in 22q11.2DS, affecting three-quarters of all diagnosed individuals.\(^2\) Notable among these are Schizophrenia-spectrum disorders; about a third of 22q11.2DS individuals develop a psychotic disorder during life, most of them by early adulthood.\(^3\) Thus, a diagnosis of 22q11.2DS constitutes a 30-fold increased risk of developing psychosis over the general population and a 10-fold elevated risk over other populations with neurodevelopmental disabilities.\(^4\) Therefore, 22q11.2DS is currently the strongest known risk factor for psychosis and a promising model for studying the etiology of schizophrenia and early signs of psychosis proneness.\(^5,6\)

As in non-deleted individuals, psychotic symptoms develop gradually in those with 22q11.2DS, and psychosis is usually preceded by subthreshold symptomology.\(^7,8\) Few studies have assessed subthreshold psychotic symptoms in 22q11.2DS reporting prevalence rates ranging from 20% to 56.5%.\(^5,9-12\) Small sample sizes, differences in participants' age, various definition of “prodromal symptoms” used (i.e., including positive symptoms, negative/disorganized symptoms, or both), and the assessment tool employed, may contribute to the variability in reported rates.

These inconsistencies call for additional investigation into the incidence and characteristics of subthreshold psychotic symptoms in 22q11.2DS from early childhood through adulthood. An analysis that is based on a large cohort of participants undergoing comparable clinical assessments is likely to provide answers to some of the questions that arise due to the limitations in the literature.

Several well-validated diagnostic tools are applied for assessing subthreshold psychotic symptoms, including the Structured Interview for Prodromal Syndromes
(SIPS). Originally developed for the evaluation of subthreshold psychotic symptoms in the general population, the SIPS has good psychometric properties, and criteria for a clinical high-risk state have been shown to predict conversion to psychosis in non-deleted populations (~20% by 1-year and 33% by 3-years). The SIPS has been effectively administered to individuals with 22q11.2DS in several studies.

Several factors may contribute to developing psychosis in individuals with 22q11.2DS. Among these are longitudinal decline in verbal IQ (VIQ), lower baseline IQ, the presence of comorbid anxiety disorders, and lower global functioning. However, the comorbidity of these conditions with subthreshold psychotic symptoms has not been sufficiently explored. Moreover, assessment of this phenomenon in 22q11.2DS individuals of various ages is vital for elucidating the rate and nature of subthreshold psychotic symptoms across development in this population.

Accordingly, the aims of the current study are: 1. To determine the rates of positive and negative/disorganized subthreshold psychotic symptoms in the largest cohort of 22q11.2DS individuals published to date; 2. To investigate (cross-sectional) changes in the prevalence of different definitions of subthreshold symptoms across development - from early childhood throughout adulthood; 3. To determine whether higher rates of psychiatric comorbidities and lower intellectual and global functioning co-occur with subthreshold psychotic symptoms.
Methods

Participants

This study represents the collaborative efforts of researchers across 10 independent medical centers worldwide, 6 in the U.S., 3 in Europe, and 1 in Israel (table 1 lists the demographics and enrollment specifications for each site). The sites are part of the International 22q11.2 Deletion Syndrome Brain Behavior Consortium (IBBC). Participants had a 22q11.2 microdeletion confirmed by molecular testing, underwent a structured clinical assessment of psychiatric psychopathologies, and completed the SIPS interview for evaluating subthreshold psychotic symptoms. Of the 839 individuals originally enrolled in the study, 79 were excluded due to missing data on the SIPS positive symptoms (>9%), resulting a total of 760 participants aged 6-55 years (mean age, 17.1±6.8).

Of the study sample (n=760), 56 participants (7.4%) were on antipsychotic medication, 118 participants (15.5%) were taking antidepressants, 26 participants (3.4%) were taking a mood-stabilizer, 34 participants (4.5%) were taking an anxiolytic medication and 104 participants (13.7%) were taking stimulants.

Each site received approval from its local ethics committee (institutional review board; IRB), and each participant or his or her legal caregiver gave written informed consent prior to study entry.

SIPS Administration and Scoring

Participants were evaluated for the presence of subthreshold psychotic symptoms by a well-trained Bachelor’s, Master’s, Doctoral, or Post-doctoral/Resident-level interviewers skilled in using the SIPS Scale of Prodromal Symptoms (SOPS).
Furthermore, all interviewers were routinely supervised by psychiatry and psychology faculty, knowledgeable in using the SIPS, at each of the participating sites.

The SOPS is composed of 19 items, each representing a different possible subthreshold psychotic symptom, yielding four constructs: Positive, Negative, Disorganized and General symptoms. Each item is rated on a seven-point scale (0-absent, 1-questionably present, 2-mild, 3-moderate, 4-moderately severe, 5-severe but not psychotic, 6-severe and psychotic/extreme).

Some items of the SIPS are more entangled with non-psychotic comorbidities. For example, D3, “trouble with focus and attention”, overlaps significantly with ADHD, and N5, poor “ideational richness”, overlaps with reduced intellectual ability. In these cases, we considered that these symptoms nevertheless might represent subthreshold psychotic symptoms. Therefore, we rated these SIPS items based on their presence and without regard to other comorbidities. As such, dual scoring was given for the same symptom of inattention in the SIPS and in the ADHD section of the K-SADS. This is consistent with the original intention of the SIPS, that items be rated without regard to diagnostic etiology.

In the majority of cases, separate interviews were conducted with probands and their caregivers, usually mothers. The SIPS was administered separately from the child to all parents of children younger than 18 years of age, as well as for parents of adult participants when possible. Younger probands (aged 6–10 years) underwent clinical evaluations probing for subjective and characteristic symptoms (including delusional and bizarre ideas, suspiciousness, grandiosity, perceptual abnormalities, disorganized speech, social anhedonia, and avolition). Probands aged 11 years and older received the full SIPS. Whenever there were discrepancies in the provided information, each responder was asked for clarification.
Establishing Reliability in Assessing Subthreshold Psychotic Symptoms between Two Participating Sites: Philadelphia and Israel

The Tel Aviv and Philadelphia sites are funded, as part of a binational prospective research project, to study psychosis risk in 22q11.2DS. Thus, the two centers conducted training sessions to ensure the consistency of SIPS administration and scoring methodology. The high inter-rater reliability achieved suggests that multi-site studies that aim to reliably assess subthreshold psychotic symptoms in individuals with 22q11.2DS are feasible. This is especially important in the context of administering the SIPS – which was originally developed for use in the general population – to individuals with neurodevelopmental and neurogenetic conditions, such as 22q11.2DS. The low IQ (and, respectively, the poor ideational richness) that characterizes many 22q11.2DS individuals makes SIPS administration a challenging task that requires skilled personnel. The international 22q11.2 Deletion Syndrome consortium is a multi-center study geared towards characterization of a large cohort of existing data sets. The retrospective nature of the project therefore focused on data harmonization and reliability is currently pursued in several sites. The following paragraph details the efforts of two sites.

The Israeli team was trained by the PI from the Philadelphia site (R.E.G) to administer the SIPS in the same manner that it is being conducted in the Philadelphia 22q11.2DS study. Consequently, in both sites the SIPS interview was conducted separately for participants and caregivers. Whenever discrepancies emerged between the 22q11.2DS and collateral informants, a combined rating was given in a consensus meeting. Four cases from the Israeli cohort were independently evaluated and given SIPS scores by R.E.G. and the clinical psychologist from the Israeli site (Y.G.).
The between-site weighted kappa intra-class correlation coefficients (ICC) for the SIPS items presented for both centers in this study ranged between very good to excellent (besides the ICC for N5, "ideational richness"): P1, “unusual thought content/delusional ideas” (ICC = 0.99), P2, “suspiciousness/persecutory ideas” (0.98), P3, “grandiosity” (0.98), P4, “perceptual abnormalities/hallucinations” (1.00), P5, “disorganized communication” (0.98), N1, “social anhedonia” (0.95), N2, “avolition” (0.95), N3, “expression of emotion” (0.98), N4, “experience of emotions and self” (1.00), N5, “ideational richness” (0.00), N6, “occupational functioning” (1.00), D1, “odd behavior or appearance” (0.97), D2, “dysphoric mood” (1.00), D3, “trouble with focus and attention” (0.89), and D4, “personal hygiene” (0.95).

*Subthreshold Psychotic Symptoms Definitions*

The spectrum of subthreshold psychotic symptoms, consistent with the deleted and none-deleted literature, was defined in four categories.\(^5,16,24\) Positive subthreshold psychotic symptoms - having one or more positive symptoms rated 3-5; *acute* positive subthreshold psychotic symptoms - having at least one positive symptom rated 6 without fulfilling criteria for a psychotic spectrum disorder; negative/disorganized subthreshold psychotic symptoms - having at least two negative/disorganized symptoms rated 3-6 (without the presence of positive subthreshold symptoms); positive and negative/disorganized subthreshold psychotic symptoms - having one or more positive symptoms rated 3-5 and at least two negative/disorganized symptoms rated 3-6.
Psychiatric Evaluation

Probands and their caregivers were interviewed by trained psychiatrists or psychologists using the Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present and Lifetime (K-SADS-PL)\textsuperscript{25} in 8 centers, the Diagnostic Interview for Children and Adolescents (DICA)\textsuperscript{26} in one center (Geneva), and the Child and Adolescent Psychiatric Assessment (CAPA)\textsuperscript{27} in another center (Cardiff). Adult participants were interviewed using the Structured Clinical Interview for Axis I DSM-IV (SCID)\textsuperscript{28} in 9 centers and the PAS-ADD clinical interview for adults\textsuperscript{29} in one center (Cardiff).

Psychiatric diagnoses were established, when appropriate, according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).\textsuperscript{30} Nearly all of the participants underwent clinical evaluation for the presence of schizophrenia spectrum disorders \((n=756; 64 \text{ fulfilled the criteria})\), anxiety disorders \((n=757; 310 \text{ fulfilled the criteria})\), mood disorders \((n=760; 133 \text{ fulfilled the criteria})\), attention deficit/hyperactivity disorders (ADHD; \(n=732; 257 \text{ fulfilled the criteria})\), oppositional defiant and conduct disorders \((n=731; 26 \text{ fulfilled the criteria})\), and substance-related disorders \((n=626; 15 \text{ fulfilled the criteria})\). Prevalence rates of psychotic disorders and other psychiatric comorbidities are detailed in table S1.

Of the 760 participants with complete data on the SIPS positive items, 68 were excluded from the statistical analysis due to fulfillment of the criteria for schizophrenia spectrum disorders \((n=64)\), or not completing clinical evaluation \((n=4)\). Consequently, the final study cohort included 692 participants aged 6-55 years (mean age, 16.9±6.7). Of them, 350 participants were males (50.6%), 429 Caucasians (62%), 235 Afro-Americans (34%), 10 of mixed ethnicity (1.4%), and 9 Hispanic (1.3%).
**Intellectual Functioning**

Age-appropriate Wechsler intelligence scales were used for assessment of intellectual functioning, including the Wechsler Preschool and Primary Scale of Intelligence (WPPSI), the Wechsler Intelligence Scale for Children-Revised (WISC-R), the Wechsler Intelligence Scale for Children-Third Edition (WISC-III), the Wechsler Abbreviated Scale of Intelligence-Second Edition (WASI-II), and the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III). A total of 521 participants (68.4%) completed the evaluation. The mean full-scale IQ (FSIQ) was 76.3±13.2 points, and the mean VIQ (assessed in 507 participants) was 79.8±13.7 points. There were 187 individuals (35.9%) with a FSIQ ≤70, consistent with intellectual disability. Age was not significantly associated with FSIQ score (Pearson $r=0.03, p=0.45$).

**Statistical Analysis**

Statistical analysis was conducted using SPSS Version 20.0. To compare the rates of subthreshold psychotic symptoms at different stages of development, the cohort was divided into 4 age groups: 6 to 12 years (children), 13 to 17 years (adolescents), 18 to 25 years (young adults), and 26 years and above (older adults). The prevalence rates of positive subthreshold psychotic symptoms (i.e., having one or more positive symptoms rated 3-5) and the combined subgroup of symptoms (i.e., having one or more positive symptoms rated 3-5 and/or at least two negative/disorganized symptoms rated 3-6) were compared between the four different age groups using the $\chi^2$ test and with Fisher exact test when the $\chi^2$ test assumptions were not met. A significant difference between all four groups was followed by post-hoc contrast analysis comparing the group with the highest rates of subthreshold symptoms (Adolescents, aged 13 – 17 y) to all other groups. The False Discovery Rate (FDR)
method for adjustment of significance level was computed using SAS for Windows version 9.4.

Univariate analysis of variance (ANOVA) was applied to examine differences in the scores of individual SIPS items between the age groups. Bonferroni post-hoc comparisons were conducted only for the items that reached statistical significance at the level of $p<0.003$ (0.05/15, with 15 representing the number of comparisons/number of SIPS items).

Next, independent t-tests were calculated to compare between (a) 22q11.2DS with positive subthreshold psychotic symptoms (i.e., having one or more positive symptoms rated 3-5) vs. those without positive subthreshold symptoms or acute positive subthreshold symptoms, and (b) 22q11.2DS with negative/disorganized subthreshold psychotic symptoms (i.e., having at least two negative/disorganized symptoms rated 3-6) vs. those without positive or negative/disorganized subthreshold symptoms. Analyses were corrected for multiple comparisons ($p$ value lower than .0062 was regarded as significant). The positive and negative/disorganized subthreshold symptoms were chosen as each of them is a risk factor for the evolution of psychotic disorders in non-deleted and deleted individuals. Potential contribution of research sites to the variability in individual items between the age groups was controlled for by including site as covariate (See Table S3).

**Results**

*Prevalence of Subthreshold Psychotic Symptoms*

Nearly one-third of participants met criteria for positive subthreshold psychotic symptoms (228/692; 32.8%), less than 1% qualified for acute positive subthreshold psychotic symptoms (6/692), and almost a quarter of participants met criteria for
negative/disorganized subthreshold psychotic symptoms where positive subthreshold psychotic symptoms were not present (140/641; 21.7%). Finally, one-fourth of participants (160/692; 25.6%) met criteria for both positive and negative/disorganized subthreshold psychotic symptoms.

About 90% of the participants who rated 6 on at least one positive SIPS item were diagnosed with a psychotic disorder (48/54) compared to 6% of those who rated 3-5 (15/242), $\chi^2(1)=180.18$, $p<0.001$, $\eta^2=.78$. Participants with both positive and negative/disorganized symptoms were more likely to be diagnosed with psychotic disorder (7/167) compared to participants who met criteria for the negative/disorganized definition solely (0/140), *Fisher exact test* = 6.00, *df* = 1, $p<0.05$.

Notably, 66.3% of the participants did not meet criteria for either positive or acute positive subthreshold psychotic symptoms (459/692). Of this group, the majority (65.9%) did not meet criteria for the negative/disorganized definition either.

The most prevalent subthreshold symptom was poor ideational richness, followed by trouble with focus and attention, avolition, and occupational functioning. The least prevalent symptoms were grandiosity and bizarre thinking. Individual item scores and subthreshold rates in the entire 22q11.2DS cohort are described in Table 2.

*Subthreshold Psychotic Symptoms from Early Childhood throughout Adulthood*

Significant differences between the age groups were found in the positive subthreshold psychotic symptoms subgroup and the combined (positive and negative/disorganized) subthreshold psychotic symptoms subgroup. Post-hoc contrast analysis using FDR for adjustment of significance level revealed significantly higher rates of positive subthreshold symptoms in adolescents compared to children, FDR = 0.039, $\chi^2(1)=6.07$, $p<0.02$, $\eta^2=.12$, and older adults, FDR = 0.047, $\chi^2(1)=4.47$, $p<0.03$. 
In the same vein, a post-hoc contrast analysis conducted for the combined subthreshold symptoms subgroup revealed higher rates in adolescence compared to children, FDR = 0.027, $\chi^2(1)=9.30$, $p<0.003$, $\eta^2=.18$, and older adults, FDR = 0.013, $\chi^2(1)=8.34$, $p<0.005$, $\eta^2=.20$. The acute positive symptoms subgroup has been diagnosed in a limited number of individuals, and it was present in children and adolescents but absent among adults (table 3).

Age-related differences in mean scores of positive, negative, and disorganized symptoms emerged. Specifically, adolescents scored higher on items: P4, “perceptual abnormalities/ hallucinations”, $F(3,686)=6.20$, $p<0.001$, $\eta^2=.02$, N1, “social anhedonia”, $F(3,616)=6.94$, $p<0.001$, $\eta^2=.03$, N3, “expression of emotion”, $F(3,617)=17.00$, $p<0.001$, $\eta^2=.07$, N4, “experience of emotions and self”, $F(3,597)=6.11$, $p<0.001$, $\eta^2=.03$, and, N5, poor “ideational richness”, $F(3,617)=17.33$, $p<0.001$, $\eta^2=.08$, compared to all or most other age groups. Finally, children and adolescents scored significantly higher on item D3, “trouble with focus and attention”, $F(3,620)=16.92$, $p<0.001$, $\eta^2=.08$, compared to the young adults and older adults groups (See figure 1 and table S2 for details).

**Psychiatric Comorbidities, Intellectual Functioning, and Global Functioning in Affected vs. Non-Affected Individuals**

The rates of anxiety disorders has been significantly higher in participants with positive subthreshold psychotic symptoms compared to those without (55.1% vs. 35.1%, $\chi^2(1)=25.54$, $p<0.001$, $\eta^2=.19$; table 4). In addition, intellectual functioning (FSIQ) and global functioning (GAF) scores were lower in subjects with positive subthreshold symptoms compared to those without (FSIQ, 74.4±12.0 vs. 78.2±13.3, $t(467)=3.01$, $p=0.002$; GAF, 57.4±12.1 vs. 69.4±46.6, $t(664)=3.83$, $p<0.001$) (table 4).
The rates of anxiety disorders and ADHD have been significantly higher in subjects with negative/disorganized subthreshold psychotic symptoms compared to those without (43.6% vs. 29.6%, \( \chi^2(1) = 7.94, p = 0.006, \eta^2 = 0.14 \), and 44.0% vs. 27.3%, \( \chi^2(1) = 10.75, p = 0.001, \eta^2 = 0.16 \), respectively; table 4). Intellectual functioning (FSIQ, VIQ) and global functioning (GAF) scores have been lower in subjects with negative/disorganized subthreshold symptoms compared to those without (FSIQ, 75.8±12.3 vs. 80.7±12.8, \( t(268) = 3.12, p = 0.002 \); VIQ, 78.3±12.7 vs. 83.3±13.7, \( t(258) = 1.77, p = 0.004 \); GAF, 60.4±14.8 vs. 71.4±11.35, \( t(384) = 8.13, p < 0.001 \), respectively).

**Discussion**

This multi-site study represents the largest cohort and the most comprehensive analysis reported to date on subthreshold psychotic symptoms in individuals with 22q11.2DS. The novel aspects of our study include an examination of the development of subthreshold psychotic symptoms by age groups, and evidence that cognitive deficits are associated with subthreshold psychosis in this population. Specifically, we show that the peak prevalence of positive subthreshold psychotic symptoms occurs during adolescence and young adulthood (ages 13 to 25 years), which is similar or slightly later than the peak occurrence of subthreshold syndrome reported in non-help-seeking typically developing individuals.\(^{36}\) Furthermore, our findings indicate that FSIQ scores are significantly lower in 22q11.2DS individuals with vs. without subthreshold psychotic symptoms. Of note, lower IQ has been associated with psychotic disorders\(^2\) and with the risk for developing psychotic disorders in 22q11.2DS.\(^7\)
Psychiatric comorbidities in 22q11.2DS are common,\textsuperscript{2} and our study provides additional evidence that conditions of subthreshold psychosis are characterized by an extent of psychiatric symptomology, including anxiety and mood disorders and higher rates of ADHD,\textsuperscript{37} coupled with lower FSIQ scores. These comorbidities are similar to those reported in non-deleted individuals.\textsuperscript{38,39} Findings in non-deleted individuals show that psychiatric disorders tend to be less specific in early stages and more so with progression.\textsuperscript{39} Notably, the majority of non-deleted individuals with subthreshold psychotic symptoms do not develop schizophrenia spectrum disorders.\textsuperscript{40} Many patients with subthreshold psychotic symptoms progress to develop other psychiatric disorders such as anxiety and affective disorders.

It is plausible that the subthreshold psychotic symptoms in 22q11.2DS are not pathognomonic since only a portion of the deleted individuals develop psychosis while many others will evolve to other psychiatric morbidities such as anxiety disorders and depression. An answer to this question will be provided by longitudinal studies that have only begun to examine the outcome of 22q11.2DS individuals with subthreshold psychotic symptoms.\textsuperscript{41} Besides the need to find the proportion of subthreshold 22q11.2DS individuals who will develop full-blown psychosis, it is also important to determine the proportion of the subthreshold 22q11.2DS individuals who will continue to cope with or will develop mood disorders, anxiety disorders and ADHD,\textsuperscript{37} as these disorders have been shown to negatively affect the quality of life and functioning of individuals with 22q11.2DS.\textsuperscript{42-44}

The collective prevalence rates of those with positive subthreshold symptoms (32.8\%) and those with negative/disorganized subthreshold symptoms (21.7\%) sum up to 54.5\%, which is similar to the 54\% who met criteria for “psychosis-proneness” in the research conducted by Tang et al., 2014.\textsuperscript{5} Similarly, the rates of
negative/disorganized subthreshold symptoms found in our cohort parallel those reported in several previous studies with 22q11.2DS individuals, suggesting that negative symptoms are common in this population.\textsuperscript{11,22}

Negative symptoms are considered important predictors of the likelihood to convert to psychosis in non-22q11.2DS high-risk populations.\textsuperscript{11,45} For example, moderate and severe subthreshold negative symptoms were highly abundant in individuals at high risk for psychosis in the North American Prodrome Longitudinal Study (NAPLS), and the severity and persistence of these symptoms were positively associated with transition rates into a psychotic state at 6- and 12-months post-baseline visits.\textsuperscript{45} Another study which assessed negative subthreshold psychotic symptoms in typically developing youths found significant associations with the participants' neurocognitive performance and functions that are central to the evolution of psychosis.\textsuperscript{46} Taken together, the accumulating evidence suggest that 22q11.2DS individuals with subthreshold negative symptoms in our study are at higher risk of transitioning into full-blown psychotic disorders.

Nevertheless, in 22q11.2DS literature, negative symptoms, most notably, ideational richness and trouble with focus and attention (i.e., ADHD), have been suggested as features of the general phenotype of the syndrome,\textsuperscript{47} regardless of the degree of the risk for psychosis. This indicates that negative symptoms may not yield the predictive power that positive symptoms may yield, particularly in adolescents who are more likely to endorse negative symptoms than children and, in some cases, adults.\textsuperscript{48} Accordingly, future studies should examine whether, and at what ages, the presence of negative subthreshold symptoms also predicts the emergence of psychosis in the 22q11.2DS population. Prospective multi-center studies are needed to adapt the SIPS to neurodevelopmental disorders with below-average IQ and excess psychiatric
comorbidities (including ADHD), as is the case with most individuals with 22q11.2DS.

A limitation of the current analysis might be related to the lack of establishing cross-site reliability of the SIPS. However, the Tel Aviv and Philadelphia sites conducted joint training sessions to ensure the consistency of SIPS administration and scoring methodology (as detailed in the Methods section). The inter-rater reliability scores achieved were excellent (besides N5, kappa scores ≥0.89), indicating the feasibility of multi-site studies that aim to reliably assess subthreshold psychotic symptoms in individuals with 22q11.2DS. The pilot inter-site reliability obtained in this study encourage conducting international multi-site training and reliability.

Another limitation may relate to the cross-sectional rather than longitudinal nature of the current study design. As such, it was not possible to identify predictive factors of symptom progression over time. The predictive value of the SIPS in terms of the likelihood of those presenting with subthreshold symptoms to transition to psychosis constitutes an important topic with marked clinical implications, and studies that examine this question are currently underway.

Moreover, there was no information on the age at onset or worsening of subthreshold psychotic symptoms in the current cohort, which undermines the ability to determine whether those with subthreshold symptoms qualify for clinical high risk or ultra-high risk status. In addition, since we used dual scoring for subthreshold psychotic symptoms measured by the SIPS and for psychiatric symptoms measured by the K-SADS the reported rates of negative/disorganized symptoms might have been inflated and the associations between subthreshold symptoms and higher rates of ADHD and lower FSIQ scores can therefore be biased. Nevertheless, at this early stage of applying the SIPS to individuals with a neurogenetic disorder, we ought to
adhere to the standard procedures. Prospective studies will need to examine these issues when adapting the SIPS to neurodevelopmental disorders considering relevant characteristics. Additionally, while the feasibility and utility of applying the SIPS to individuals with 22q11.2DS at various stages of development were supported by this study, there is still a need to standardize the methodology of its administration and verify its reliability in the context of 22q11.2DS subthreshold psychosis before it can be recommended for widespread clinical implementation.

In conclusion, the present study indicates that nearly a third of 22q11.2DS individuals meet criteria for positive subthreshold psychotic symptoms and almost a quarter meet criteria for negative/disorganized subthreshold symptoms, with adolescents and young adults showing the highest rates of subthreshold symptoms. We found that 22q11.2DS individuals with subthreshold psychotic disorders have high rates of anxiety disorders and ADHD lower IQ and more impaired functioning. Future longitudinal studies would demonstrate the predictive value of 22q11.2DS subthreshold psychotic symptoms and its associated features in the context of the propensity to transition to psychosis.
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Figure Legends:

**Figure 1.** Comparison of the Mean Scores of Individual SIPS Items Between the Four 22q11.2 Deletion Syndrome Age Groups;

Mean+SEM; ** $p<.01$; *** $p<.001$. 
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