Title: Attention Deficit Hyperactivity Disorder symptoms and psychosis in 22q11.2 Deletion syndrome

Running title: ADHD and psychosis in 22q11.2DS

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Abstract

Objective: 22q11.2 Deletion Syndrome (22q11.2DS) is associated with increased risk for schizophrenia in adulthood while ADHD is the most prevalent diagnosis in childhood. Inattention symptoms are pronounced in 22q11.2DS and given that attentional impairment is a core feature of schizophrenia, inattention symptoms may reflect underlying ADHD, psychosis, or both. We investigate whether inattention is associated with psychosis in 22q11.2DS and in other groups at risk for psychosis but without the deletion (ND) (idiopathic clinical risk and first degree family members of individuals with schizophrenia).

Methods: 137 individuals with 22q11.2DS (mean age: 14.0), 84 ND individuals with subthreshold psychosis (mean age: 16.9) and 31 ND individuals with family history of psychosis (mean age: 17.0) were included in the study. Psychopathology was assessed using research diagnostic assessments.

Results: ADHD total symptoms were associated with overall levels of subthreshold psychosis symptoms in 22q11.2DS (β=0.8, p=0.04). Inattention symptoms were specifically associated with positive (β=0.5, p=0.004), negative (β=0.5, p=0.03), and disorganized (β=0.5, p<0.001) symptoms, while hyperactivity-impulsivity symptoms were associated with disorganized symptoms (β=0.5, p=0.04). The prevalence of ADHD inattention symptoms was higher in 22q11.2DS with subthreshold psychosis compared to ND individuals with subthreshold psychosis (p<0.001), even when adjusting for cognitive impairment and overall psychopathology. The pattern was similar when comparing individuals with 22q11.2DS and ND individuals with family history of psychosis.

Conclusions: This is the first study to examine the associations between ADHD and psychosis in 22q11.2DS. Our findings support a potentially important role of ADHD inattention symptoms in psychosis in 22q11.2DS.

Keywords: schizophrenia, hyperactivity, impulsivity, inattention

Attention Deficit Hyperactivity Disorder symptoms and psychosis in 22q11.2 Deletion syndrome

Introduction

22q11.2 Deletion Syndrome (22q11.2DS) is a chromosomal disorder caused by a microdeletion of ~40 genes. It has been associated with multiple physical manifestations, most related to disruptions of neural crest development[1, 2]. 22q11.2DS is also one of the strongest known genetic risk factors for schizophrenia, associated with about a 30% increased risk of developing this disorder in adulthood[3]. Children with 22q11.2DS have been reported to be at risk for developing a range of psychiatric disorders, including autism, Oppositional Defiant Disorder (ODD) and anxiety disorders [3-5]. Attention Deficit Hyperactivity Disorder (ADHD) is the most prevalent childhood psychiatric disorder with reported rates estimated at 37%[3] compared to 2-6% in the general population[6]. Studies comparing features of ADHD between 22q11.2DS and individuals without the deletion have indicated that inattention symptoms in 22q11.2DS are pronounced[7, 8]. Such symptoms include difficulties focusing and sustaining attention, difficulties with organizing tasks, easily forgetting and losing things, and may reflect attentional and working memory dysfunction[9].

Notably, inattention is a core symptom of both ADHD and schizophrenia[10]. Attentional impairment has been long recognized as a core characteristic of schizophrenia, where

clinically relevant symptoms of inattention are often present (e.g.[11]). Studies of childhood onset schizophrenia have indicated prevalent premorbid ADHD-like symptoms[12-14]. Increased rates of inattentive symptoms have also been reported in clinical[15, 16] and non-clinical samples[17, 18] of individuals with prodromal symptoms of psychosis, as well as in individuals at genetic risk due to family history[19]. These findings support that attentional impairments are evident early in the course of the illness and/or are associated with genetic liability to psychosis.

In light of this evidence, it is possible that the high prevalence of inattention symptoms in 22q11.2DS may reflect additional emerging risk for psychosis or it could be that 22q11.2DS increases risk for both ADHD and psychosis. Given that attentional impairment is also taken into account for the diagnosis of schizophrenia, it is important to disentangle this symptom overlap with ADHD as this can improve our understanding of risk for schizophrenia in 22q11.2DS. Moreover, if ADHD inattention symptoms are associated with genetic liability to psychosis, their earlier manifestation in relation to psychosis could indicate that they are on the pathway between genetic risk and schizophrenia in 22q11.2DS. This can have potentially important implications for prevention and treatment in 22q11.2DS as well as for future genetic studies. Although a previous study did not find evidence that ADHD is associated with development of psychosis[20], the sample was small (n=28) and the study examined only diagnoses, rather than ADHD symptoms. The evidence is weak for a role of ADHD in psychosis in populations without the deletion. A longitudinal follow-up study on over 200 children with ADHD suggested an increased risk of schizophrenia in adulthood[21], but other

longitudinal studies have not found such associations[22-24]. Our prior work examining comorbidity in 22q11.2DS found that among participants with 22q11.2DS and ADHD, 64.1% also had psychosis spectrum disorders and 41% of 22q11.2DS participants with psychosis spectrum disorders had ADHD[25], a finding that indicates a potential role for ADHD in the development of psychosis in 22q11.2DS. The current study with the same 22q11.2DS participants extends these findings as the first to examine whether particular ADHD symptoms, are associated with subthreshold psychosis symptoms in individuals with 22q11.2DS.

Another way to investigate whether the ADHD inattention symptoms are associated with genetic liability to psychosis in 22q11.2DS is to compare their prevalence with that of individuals without the deletion (ND) who are also at high risk of psychosis. Previous studies have examined either the prevalence of ADHD inattention symptoms in relation to ADHD hyperactivity-impulsivity symptoms within 22q11.2DS[26, 27] or the prevalence of ADHD inattention symptoms when compared to ND ADHD samples[7, 8]. However, no study has directly compared the prevalence of ADHD symptoms in 22q11.2DS with other groups with increased risk for psychosis, including youths with subthreshold psychosis symptoms and first-degree relatives of individuals with psychosis. Examining the prevalence of ADHD symptoms in these groups can help understand how these symptoms relate to risk for psychosis in 22q11.2DS. If these ADHD symptoms, particularly inattentive, are associated with genetic liability for psychosis, then their prevalence should be analogous to the extent of risk for psychosis in populations at high risk for psychosis. Considering that risk for psychosis is higher in 22q11.2DS relative to

individuals with subthreshold psychosis[28] and family history of psychosis[29], then the prevalence of ADHD inattention symptoms would also be higher in individuals with 22q11.2DS in comparison with the ND groups.

The main goals of this study were: 1) examine whether ADHD symptoms are associated with subthreshold psychosis symptoms in individuals with 22q11.2DS. We hypothesized that ADHD symptoms, particularly ADHD inattention symptoms, would be associated with psychosis spectrum symptoms in individuals with 22q11.2DS; 2) compare the prevalence of ADHD symptoms between the following groups: a) individuals with 22q11.2DS and subthreshold psychosis symptoms and ND individuals with subthreshold psychosis symptoms and b) individuals with 22q11.2DS and ND individuals with a family history of psychosis. We hypothesized that the frequency of ADHD inattention symptoms would be higher in individuals with 22q11.2DS in comparison with the ND groups.

To address these aims we conducted one of the largest studies of individuals with 22q11.2DS and we also evaluated ND groups who were assessed using the same detailed phenotypic assessments.

Method

Samples

Participants, with 22q11.2DS and ND, were selected from two ongoing prospective studies that used the same phenotypic assessments to enable direct comparisons. Both groups were recruited from medical clinics and community sources. Individuals with 22q11.2DS were selected based on the deletion whereas the ND group was selected from a larger pool that was community screened and then selected for longitudinal evaluation based on the presence or absence of subthreshold psychosis symptoms at baseline, as described previously[4, 30-32]. A total of 137 individuals with 22q11.2DS were included in the study. A subset of 72 individuals with 22q11.2DS were classified as having significant subthreshold psychosis symptoms (see[31]), and they were compared with 84 ND individuals, also with subthreshold psychosis symptoms[33]. This comparison was made in order to compare two groups that are at clinical high risk for psychosis based on existing symptoms.

The entire sample of 22q11.2DS was compared to 31 ND individuals with family history of psychosis, in a first-degree relative as assessed by an abbreviated version of the Family Interview for Genetics Studies[34] using procedures described by Calkins et al[33]. This allows comparison of one genetic model for psychosis risk (22q11.2DS confers genetic risk for psychosis, whether or not psychosis symptoms are currently present) against another (individuals with family history of psychosis have genetic risk for psychosis regardless of whether they are currently symptomatic).

The Institutional Review Boards of the University of Pennsylvania and the Children's Hospital of Philadelphia (CHOP) approved the study. Informed consent/assent was obtained from adult participants and from caretakers of younger participants with their assent.

Measures

A modified version of the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS)[35] was administered to obtain DSM-IV-TR diagnoses of ADHD for both 22q11.2DS and non-deleted samples. The K-SADS is a semi-structured interview that assesses categorical diagnoses as well as symptom counts of psychiatric disorders, including ADHD. We examined ADHD inattention, hyperactivity-impulsivity and total symptoms. Although ADHD symptoms were the focus of the study, we also examined the categorical DSM-IV-TR ADHD diagnosis.

The Structured Interview for Prodromal Syndromes (SIPS)[36] was used to obtain Scale of Prodromal Symptoms (SOPS) ratings of positive, negative, disorganized and general symptoms. Individuals were classified as "subthreshold psychosis" based on significant positive, negative and/or disorganized symptoms as previously described[25, 31, 33]. Specifically, "subthreshold psychosis" diagnoses were given if the individuals reported at least 1 positive symptom rated >=3 or at least 2 negative and/or disorganized symptoms rated >=3. Interviews were conducted by experienced and trained clinical assessors who were supervised by clinical investigators. SOPS symptom ratings and

DSM-IV-TR diagnoses of psychotic disorders and ADHD were achieved via case conference consensus review by at least two doctoral level clinicians.

Reading proficiency was estimated using the Wide Range Achievement Test -4 (WRAT-4) Reading subtest, which assesses the ability to recognize and pronounce words, listed in order of increasing vocal complexity and difficulty[37]. We also obtained a composite measure of executive function from the Penn computerized Neurocognitive Battery[38-40]. It included the Penn Conditional Exclusion Test (PCET) and the Penn Letter N-back Test (NBACK). We did not formally assess IQ in our study.

Data analysis

Data analyses were conducted with Stata (version 13)[41]. Linear regressions within the 22q11.2DS group examined the associations between ADHD scores and SOPS. Student's t-tests or, in the case of non-normally distributed variables, Mann-Whitney U tests, were applied to compare demographic and clinical variables as well as symptom counts. Chi-square tests were used to compare the rates of ADHD diagnosis between the groups. As a supplementary analysis, the Wilcoxon matched-pairs signed-rank test was used to examine whether the ADHD diagnosis and symptom counts were similar between the 22q11.2DS and individuals without a deletion with family history of psychosis after matching for sex and age. To account for the potential confounding effects of age, reading proficiency, executive functioning and total SOPS on the ADHD symptom scores, the former were regressed out of the ADHD symptom scores before

performing analyses. Specifically, using regression, each ADHD symptom score was predicted using age, age-squared, age-cubed, WRAT 4, composite executive score and total SOPS. The residuals of this analysis therefore reflected ADHD symptomatology above or below what would be expected given one's age, reading proficiency, executive functioning and total SOPS. We excluded symptom D3 (significant attentional impairments) from SOPS total, to avoid over-adjusting. Analyses were repeated to only include Caucasians in order to exclude potential confounding due to race differences.

Results

Aim 1. Associations between ADHD symptoms, psychosis spectrum symptoms and psychosis in 22q11.2DS (Table 1)

ADHD inattention symptoms were associated with positive symptoms (Cohen's f^2=0.07, p=0.004), negative symptoms (Cohen's f^2=0.04, p=0.03), disorganized symptoms (Cohen's f^2=0.11, p<0.001), total SOPS symptoms (Cohen's f^2=0.06, p=0.01) and with subthreshold psychosis (Odds Ratio (OR)=1.18, p=0.004). There was no evidence for associations between ADHD inattention symptoms and general symptoms (Cohen's f^2=0.01, p=0.22), threshold diagnoses of schizophrenia (OR=1.5, p=0.18) or other psychotic disorders (OR=1.05, p=0.71).

ADHD hyperactivity-impulsivity symptoms were associated with disorganized symptoms (Cohen's f^2=0.06, p=0.01) and with subthreshold psychosis classification (OR=1.21, p=0.01). There was no evidence for associations with positive symptoms (Cohen's f^2=0.00, p=0.64), negative symptoms (Cohen's f^2=0.00, p=0.78), general symptoms (Cohen's f^2=0.02, p=0.17), total SOPS symptoms (Cohen's f^2=0.01, p=0.24), schizophrenia (OR=1.1, p=0.66) or other psychotic disorders (OR=1.1, p=0.63).

ADHD total symptoms were associated with disorganized symptoms (Cohen's f^2=0.10, p<0.001), total SOPS (Cohen's f^2=0.04, p=0.04) and subthreshold psychosis (OR=1.12, p=0.003) while there was weak evidence for association with positive symptoms (Cohen's f^2=0.02, p=0.09) but no evidence for association with negative symptoms

(Cohen's f^2=0.01, p=0.24), general symptoms (Cohen's f^2=0.02, p=0.18), schizophrenia (OR=1.12, p=0.31) or psychotic disorders (OR=1.00, p=0.98).

Aim 2a. Comparisons of ADHD symptomatology between individuals with 22q11.2DS and subthreshold psychosis and ND individuals with subthreshold psychosis (Table 2)

The 22q11.2DS subthreshold psychosis sample was on average younger than the ND subthreshold psychosis sample (Cohen's d=-0.88, p<0.001), while there were no sex differences (Cohen's d=0.16, p=0.32). Although the estimated household income was higher in 22q11.2DS individuals (Cohen's d=0.76, p<0.001) there were no differences at the maternal education level (Cohen's d= 0.26, p=0.06) in relation to the ND sample with subthreshold psychosis. However, the 22q11.2DS subthreshold psychosis sample had lower WRAT4 scores (Cohen's d=-1.89, p<0.001) and had lower performance on the composite executive function measure (Cohen's d=-1.43, p<0.001). 22q11.2DS subthreshold psychosis sample reported less positive symptoms (Cohen's d=-0.43, p=0.01), more negative (Cohen's d=0.53, p=0.001), more disorganized (Cohen's d=0.49, p=0.003), more general (Cohen's d=0.82, p<0.001) and more total SOPS (Cohen's d=0.50, p=0.003) in relation to ND individuals with subthreshold psychosis. 22q11.2DS subthreshold psychosis sample exhibited more ADHD inattention symptoms (Cohen's d=0.95, p<0.001), more ADHD hyperactivity-impulsivity symptoms (Cohen's d=0.54, p=0.004) and more ADHD total symptoms (Cohen's d=0.75, p<0.001) relative to the ND individuals with subthreshold psychosis. These differences remained for the ADHD inattention symptoms and the ADHD total symptoms but disappeared for the

ADHD hyperactivity-impulsivity symptoms when age, WRAT4, composite executive scores and total SOPS were taken into account.
Supplementary analyses restricted to the Caucasian subsamples yielded similar results (Table S1).

Aim 2b. Comparisons of ADHD symptomatology between individuals with 22q11.2DS and ND individuals with family history of psychosis (table 3)

The 22q11.2DS sample was on average younger than the ND sample with family history of psychosis (Cohen's d=-0.72, p<0.001), while there were no sex differences (Cohen's d=0.12, p=0.50). The estimated household income was higher in 22q11.2DS individuals (Cohen's d=1.05, p<0.001) as was maternal education level (Cohen's d= 0.71, p<0.001) in relation to the ND sample with family history. However, the 22q11.2DS sample had lower WRAT4 scores (Cohen's d=-0.89, p=0.002) and performed worse on the composite executive function measure (Cohen's d=-1.49, p<0.001). The 22q11.2DS sample exhibited fewer positive (Cohen's d=-0.35, p=0.04), more negative (Cohen's d=0.41, p=0.005) and more general symptoms (Cohen's d=0.48, p=0.004) compared to ND individuals with family history of psychosis. No differences were found with regards to disorganized and total SOPS.
The 22q11.2DS sample had more ADHD inattention symptoms (Cohen's d=0.86, p<0.001), more ADHD hyperactivity–impulsivity symptoms (Cohen's d=0.68, p<0.004) and more ADHD total symptoms (Cohen's d=0.81, p<0.001). These differences remained for the ADHD inattention symptoms and the ADHD total symptoms but

disappeared for the ADHD hyperactivity-impulsivity symptoms when age, WRAT4, composite executive scores and SOPS were taken into account. The findings examining only the Caucasian subsamples and when matched for age and sex comparisons between individuals with 22q11.2DS and ND individuals with family history of psychosis were similar to the main analysis (Supplemental Tables S2 and S3).

Discussion

This is the first study to examine the associations between ADHD symptoms and psychosis symptoms in 22q11.2DS. ADHD symptoms, including inattention and hyperactivity–impulsivity, were associated with overall subthreshold psychosis classification, while inattention symptoms were also associated with positive, negative, and disorganized symptoms. Hyperactivity-impulsivity symptoms were associated only with disorganized symptoms. The prevalence of ADHD inattention symptoms was higher in individuals with 22q11.2DS and subthreshold psychosis in relation to ND individuals with subthreshold psychosis even when adjusting for reading proficiency, overall executive function and SOPS, while there was only weak evidence for higher prevalence of ADHD hyperactivity-impulsivity symptoms. The pattern was similar when comparing individuals with 22q11.2DS with ND individuals with family history of psychosis.

ADHD inattention symptoms and psychosis

Our hypothesis that ADHD inattention symptoms would be associated with psychosis spectrum symptoms in individuals with 22q11.2DS was supported. While these symptoms were not associated with schizophrenia or psychotic disorders in 22q11.2DS, this may be due to low power given that schizophrenia and psychosis were present in only 3% and 5% of the sample, respectively.

Our findings accord with previous studies in the general population[17, 18] and other clinical samples[15, 16] that have suggested a role for ADHD in psychosis. Interestingly, the prevalence of the inattention symptoms was higher in individuals with 22q11.2DS when compared to individuals with family history of psychosis. Although family history of psychosis confers genetic risk for psychosis, the risk rates are much lower in relation to the rates reported in 22q11.2DS[42], therefore, lower prevalence of inattention symptoms in this group when compared to 22q11.2DS could indicate that inattention symptoms are related to genetic risk for psychosis. Although genetic studies have not examined the shared genetic underpinnings of ADHD inattention symptoms and schizophrenia, there is evidence for shared genetic susceptibility between ADHD and schizophrenia [43] as well as for rare CNVs[44] contributing to both.

There are at least three possible explanations for the observed findings.

First, inattentive symptoms might be on a common pathway leading from genetic risk to the development of inattentive symptoms and consequently to the development of ADHD and schizophrenia[10].

Second, it is possible that ADHD inattention symptoms in the context of, or preceding other subthreshold psychosis symptoms, are phenomenologically similar to ADHD-like behaviors but reflect a premorbid or prodromal form of schizophrenia risk rather than ADHD per se. Cornblatt and colleagues (1994) suggested a model that can explain how attentional dysfunction can trigger psychosis[45]. According to this model, inattention problems can lead to defective processing of social cues that can result in deficient social skills that in turn can make social interactions particularly stressful. This could potentially lead to avoidance of interactions as a way to control symptoms. Conversely,

interactions could be sought that elicit stress and exacerbate developing symptoms. Finally, it is possible that the association between inattention symptoms and psychosis symptoms is the result of shared genetic variance and that this association results from pleiotropic genetic effects. Genetic and longitudinal studies are needed to improve our understanding of the potential mechanisms underlying risk for ADHD and schizophrenia.

Importantly, the differences in rates of ADHD inattention symptoms between individuals with the 22q11DS and ND remained despite controlling for reading proficiency and executive function that have been associated with risk for ADHD[46]. Studies have indicated that ADHD symptoms might not be unique to ADHD and instead could be associated with other psychiatric problems[47, 48]. Our recent confirmatory analysis of psychopathology in 22q11.2DS[49] indicated that, similar to populations without a deletion, psychopathology was divided into one 'general psychopathology' (p factor[50]) and four specific dimensions, including ADHD. It could therefore be that these ADHD symptoms indicate a more general vulnerability to psychopathology that is potentially over and above the cognitive deficits that underlie risk for ADHD in 22q11.2DS. Our findings however, could also indicate that the cognitive measures we used were not sensitive enough to capture the cognitive deficit that underlies these symptoms.

Weak evidence for associations of ADHD hyperactivity-impulsivity symptoms with psychosis

Although ADHD hyperactivity-impulsivity symptoms were associated with subthreshold psychosis in 22q11.2DS, the comparisons of their prevalence between the 22q11.2DS and the ND at risk groups did not support a strong role of hyperactivity–impulsivity in psychosis in 22q11.2DS. This is in accordance with a previous birth-cohort study that did not find evidence of a link between psychotic symptoms and hyperactive symptoms[17]. One explanation could be the different role that dopaminergic function plays in schizophrenia and ADHD. Dopamine is one of the main neurotransmitters that is considered to be involved in the pathophysiology of both schizophrenia and ADHD[51]. Dopaminergic hypoactivity in the brain is the most likely cause of ADHD[52] and is mostly related to impulsivity[53, 54]. Dopaminergic imbalance[55], which resembles dopaminergic hyperactivity[56, 57], has been mostly related to the positive psychotic symptoms of schizophrenia. Thus, the absence of evidence for associations between ADHD hyperactivity-impulsivity and psychosis in our sample could be due to different biological mechanisms underlying these traits. Alternatively, we cannot exclude the possibility of Type II error in our findings.

Finally, total symptoms were also associated with psychosis spectrum symptoms, a finding which accords with findings from a population based study that indicated a longitudinal association between ADHD combined subtype at age 7 and psychotic symptoms at age 12[58]. Interestingly, this study did not find longitudinal associations between the inattentive and hyperactive subtype of ADHD and later development of psychotic disorder.

Theoretical and clinical implications

Our findings have potentially important theoretical and clinical implications. The cross-sectional associations between ADHD inattention symptoms and psychosis spectrum symptoms indicate that a longitudinal study to examine these associations is warranted. If ADHD inattention symptoms are antecedents of psychosis spectrum symptoms in 22q11.2DS, then assessing these readily observable symptoms may aid detection of those individuals with 22q11.2DS who are at particularly high-risk for psychosis. Similarly, our findings indicate that individuals with 22q11.2DS with psychosis symptoms might also have ADHD inattention symptoms that need to be addressed given that ADHD inattention symptoms can pose an additional impediment to the individuals' emotional, social and occupational well-being[59, 60]. Our findings are also consistent with the NIMH Research Domain Criteria (RDoC) initiative as they indicate the importance of examining psychopathology not only in diagnostic categories but also dimensionally, as using the former might be missing individuals who are at risk but do not meet the diagnostic cut-offs[60]. Another potential clinical implication relates to the diagnosis and treatment of ADHD. Stimulants that are usually prescribed for ADHD have potentially opposing action in relation to antipsychotic medication taking into account the former act as dopamine agonists while the latter as dopamine antagonists[61]. If these ADHD inattention symptoms are also part of prodromal psychosis in 22q11.2DS, then future studies should examine the longitudinal effects of stimulant treatment as they might potentiate or alter the course of psychosis symptoms in someone who is vulnerable[62, 63].

Moreover, if ADHD symptoms are antecedents of psychosis, studies should examine whether non-pharmacological treatments addressing ADHD symptoms in childhood can potentially reduce risk for later psychosis in addition to improving function. Further longitudinal and sufficiently powered studies using detailed phenotypic assessments are needed to replicate our findings.

Strengths and limitations

This is one of the largest studies of individuals with 22q11.2DS that also includes large samples of ND high-risk comparison groups. The additional strength of our study is that the phenotypic assessments were the same between the groups, allowing for comparisons. While 86% of the individuals with 22q11.2DS were Caucasian, which is in accordance with previous studies of this disorder[3], only 68% of the ND individuals with subthreshold psychosis and 71% of the ND individuals with family history of psychosis were Caucasian. Our supplementary analyses restricted to Caucasians, though necessarily less powerful, yielded similar findings as the total sample. Moreover, there were socioeconomic differences between the samples, with the 22q11.2DS group having higher estimated household income and higher maternal education levels. However, these differences are more likely to have led to an underestimation in observed associations. Another limitation is the cross-sectional nature of the study that does not allow us to delineate whether these inattention symptoms are antecedents or correlates of psychotic phenomena. Additionally, although we adjusted for WRAT4, an approximation of IQ, and executive function, we did not adjust for IQ using IQ specific measures making it possible that some portion of the observed attention effects may be

associated with the comparatively lower IQ in participants with 22q11.2DS. Finally, because our sample with individuals with 22q11.2DS also included children who are less likely to be diagnosed with psychosis, our results may again underestimate the magnitude of the associations between inattention and psychosis symptoms.

An important consideration when interpreting these findings is that, in the subthreshold psychosis comparisons between 22q11.2DS and ND individuals, significant attentional impairment (SOPS item D3) is one of the symptoms that can contribute to a subthreshold psychosis classification. This reflects the common symptom of inattention in both “prodromal” and ADHD diagnoses, but including this item in the diagnostic classification for subthreshold psychosis might have led to the selection of a sample with overall higher prevalence of inattention symptoms. Nonetheless, because this criterion was applied to both 22q11.2DS and ND groups, it cannot influence the comparisons of the prevalence of ADHD symptoms between the two groups. Moreover, we did not include individuals without a deletion and without a family history of psychosis because an unbiased sample without family history of psychosis was not available. All of our ND individuals were selected on the presence or absence of psychosis spectrum symptoms, and psychosis spectrum symptoms have been associated with positive family history of psychosis. However, presence of psychosis family history is not necessary for the subsequent development of psychotic disorders and therefore our ND samples might not be representative of the population of individuals with psychosis.

Conclusions

We examined the associations between ADHD symptoms and subthreshold psychosis symptoms in 22q11.2DS. Our findings indicated that ADHD symptoms, particularly inattentive, were associated with subthreshold psychosis in 22q11.2DS. ADHD inattention symptoms were present at higher rates in 22q11.2DS, compared to ND individuals with subthreshold psychosis and ND individuals with family history of psychosis, further supporting a potentially important role of ADHD inattention symptoms in psychosis in 22q11.2DS. Our results also highlight the significance of employing a dimensional approach in addition to diagnostic categories. Further longitudinal studies are needed to replicate our findings as a potentially causal role of ADHD inattention symptoms in psychosis in 22q11.2DS can have important implications for prevention and treatment of psychosis in 22q11.2DS as well as beyond this syndrome.

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Supplemental material

STable 1. Supplementary analysis examining only Caucasians: Comparisons of ADHD symptomatology between individuals with 22q11.2DS and subthreshold psychosis and individuals without the deletion with subthreshold psychosis.

Variable	**22q11.2DS and subthreshold psychosis (n=62)**	**ND subthreshold psychosis (n=27)**		
	Mean(SD)/range	**Mean(SD)/range**	**χ^2, z**	**P**
Age	**14.1(4.1)/8-23**	**16.5(2.8)/11-22**	**8.21**	**0.004**
WRAT4	**42.7(10.6)/19-60**	**52.2(8.3)/27-63**	**3.81**	**p<0.001**
Executive	**-0.63(1.04)/-3.5-0.59**	**0.65(0.7)/-1.2-1.6**	**4.15**	**p<0.001**
	N(%)	**N(%)**	**χ^2**	**P**
Gender (males)(%)	34(55)	17(63)	0.51	0.48
ADHD diagnosis	**32(52)**	**8(30)**	**3.67**	**0.06**
	Mean(SD)	**Mean(SD)**	**z**	**P**
ADHD inattention symptoms	**5.9(2.9)**	**4.1(3.0)**	**-2.59**	**0.01**
ADHD hyperactivity-impulsivity symptoms	3.2(2.7)	2.5(2.4)	-0.87	0.39
ADHD total symptoms	8.5(4.8)	6.5(4.5)	-1.73	0.08
Abbreviations: ND: individuals without the deletion, ADHD-Attention Deficit Hyperactivity Disorder, WRAT4- Wide Range Achievement Test 4.				

STable 2. Supplementary analysis examining only Caucasians: Comparisons of ADHD symptomatology between individuals with 22q11.2DS and individuals without the deletion with family history of psychosis.

Variable		**22q11.2DS (n=118)**	**Family history of psychosis (n=9)**		
		Mean(SD)/range	**Mean(SD)/range**	**χ^2, z**	**p**
Age		**14.1(4.5)/8-24**	**16.0(1.6)/14-19**	**2.46**	**p<0.001**
WRAT4		42.5(11.2)/16-62	53.3(5.7)/48-60	1.90	0.06
Executive		**-0.66(1.1)/-3.5-0.9**	**0.89(0.3)/0.6-1.2**	**3.09**	**0.002**
		N(%)	**N(%)**	**χ^2**	**p**
Gender (males)(%)		62(53)	5(56)	0.03	0.86
Diagnosis	**Schizophrenia**	3(3)	0(0)	0.24	0.62
	Psychosis	4(4)	0(0)	0.32	0.57
	Subthreshold psychosis	62(54)	4(44)	0.30	0.58
	ADHD	**53(46)**	**1(11)**	**4.15**	**0.04**
		Mean(SD)	**Mean(SD)**	**Z**	**p**
ADHD inattention symptoms		**5.28(3.3)**	**2.67(3.5)**	**-2.23**	**0.03**
ADHD hyperactivity- impulsivity symptoms		**2.75(2.7)**	**0.63(1.4)**	**-2.30**	**0.02**
ADHD total symptoms		**7.59(5.0)**	**3.22(4.1)**	**-2.40**	**0.02**

Abbreviations: ADHD-Attention Deficit Hyperactivity Disorder, WRAT4- Wide Range Achievement Test 4.

STable 3. Matched age and gender comparisons of ADHD symptomatology between individuals with 22q11.2DS and individuals without the deletion with family history of psychosis.

Variable	**22q11.2DS (n=31)**	**Family history of psychosis (n=31)**		
	Mean(SD)/range		**χ^2, z**	**p**
Age	17.0(2.3)/11-23			
WRAT	0.19(0.2)/-1.7-1.4	0.5(0.5)/-1.0-1.8	**1.8**	**0.07**
Executive	**-0.27(0.4)/-0.7-0.6**	**0.8(0.4)/-0.1-1.4**	**2.02**	**0.04**
	N(%)			
Gender (males)(%)	14 (4)		**χ^2**	**p**
ADHD diagnosis(%)	13(42)	3(10)	**0.8**	**0.36**
	Mean(SD)	**Mean(SD)**	**z**	**p**
ADHD inattention symptoms	**5.4(3.5)**	**2.7(2.8)**	**-2.5**	**0.01**
ADHD hyperactivity - impulsivity symptoms	1.9(2.5)	1.2(2.0)	-0.4	0.68
ADHD total symptoms	**7.0(4.6)**	**3.9(4.0)**	**-2.2**	**0.03**
Abbreviations: ADHD-Attention Deficit Hyperactivity Disorder, WRAT4- Wide Range Achievement Test 4.				

Table 1. The relationship between ADHD symptoms, SOPS symptoms, and psychosis in individuals with 22q11.2DS.

	ADHD inattention symptoms			**ADHD hyperactivity- impulsivity symptoms**			**ADHD total symptoms**		
	Coefficient(95%CI)	**Cohen's f^2**	**p**	**Coefficient(95%CI)**	**Cohen's f^2**	**p**	**Coefficient(95%CI)**	**Cohen's f^2**	**p**
SOPS symptoms									
Positive	**0.52(0.17-0.86)**	**0.07**	**0.004**	0.10(-0.33-0.54)	0.00	0.64	0.19(-0.03-0.41)	0.02	0.09
Negative	**0.49(0.06-0.93)**	**0.04**	**0.03**	0.08(-0.48-0.64)	0.00	0.78	0.16(-0.11-0.44)	0.01	0.24
Disorganized	**0.52(0.24-0.81)**	**0.11**	**p<0.001**	**0.48(0.11-0.85)**	**0.06**	**0.01**	**0.32(0.14-0.50)**	**0.10**	**p<0.001**
General	0.21(-0.13-0.55)	0.01	0.22	0.30(-0.13-0.73)	0.02	0.17	0.15(-0.07-0.36)	0.02	0.18
Total SOPS	**1.74(0.49-2.99)**	**0.06**	**0.01**	0.96(-0.65-2.58)	0.01	0.24	**0.82(0.02-1.61)**	**0.04**	**0.04**
Diagnoses	**Odds ratio (95%CI)**		**p**	**Odds ratio (95%CI)**		**p**	**Odds ratio (95%CI)**		**p**
Subthreshold psychosis	**1.18(1.05-1.31)**		**0.004**	**1.21(1.04-1.40)**		**0.01**	**1.12(1.04-1.20)**		**0.003**
Schizophrenia	1.47(0.83-2.60)		0.182	1.10(0.73-1.66)		0.66	1.12(0.90-1.39)		0.31
Psychosis Diagnosis	1.05(0.81-1.38)		0.71	0.92(0.65-1.30)		0.63	1.00(0.85-1.17)		0.98

Abbreviations: SOPS= Scale of Prodromal Symptoms, ADHD=Attention Deficit Hyperactivity Disorder

Notes: Linear regression analyses where SOPS symptoms/Diagnoses are the outcome variable and ADHD symptoms are the predictor variable. Psychosis Diagnosis = all non-schizophrenia psychotic disorders and mood disorders with psychotic features.

Table 2. Comparisons of ADHD symptomatology between individuals with 22q11.2DS and subthreshold psychosis and individuals without the deletion with subthreshold psychosis.

Variable		**22q11.2DS PS+ (n=72)**	**ND PS+ (n=84)**									
		Mean(SD)/range	**Mean(SD)/range**	**χ^2, z**	**p**	**Cohen's d**						
Age		**13.9(4.1)/8 to 23**	**16.9(2.7)/11-23**	**-24.2**	**<0.001**	**-0.88**						
WRAT4		**-0.4(1.0)/-2.5-1.2**	**1.3(0.8)/-1.9-1.8**	**-4.2**	**<0.001**	**-1.89**						
Executive		**-0.8(1.1)/-3.5-0.6**	**0.5(0.7)/-2.0-2.1**	**-5.1**	**<0.001**	**-1.43**						
		Mean(SD)	**Mean(SD)**	**χ^2, z**	**p**	**Cohen's d**						
Estimated household income ($)		**69644(27611)**	**48631(27655)**	**32.6**	**<0.001**	**0.76**						
Maternal education level		15.0(2.3)	14.4(2.4)	3.5	0.06	0.26						
		N(%)	**N(%)**	**χ^2**	**p**							
Gender (males)(%)		40(56)	40(48)	0.98	0.32	0.16						
Race:	**Caucasian**	**62(86)**	**27(32)**									
	African-American	**4(6)**	**46(55)**									
	Mixed	**2(3)**	**0(0)**									
	Asian	**4(5)**	**11(13)**	**53.71**	**<0.001**	**-0.77**						
ADHD diagnosis		**41(57)**	**16(19)**	**25.0**	**<0.001**	**0.87**						
SOPS symptoms												
Positive		**6.5(4.6)**	**8.5(4.6)**	**-2.7**	**0.01**	**-0.43**						
Negative		**11.0(4.6)**	**8.3(5.5)**	**3.3**	**0.001**	**0.53**						
Disorganized		**5.5(3.1)**	**4.0(3.0)**	**3.0**	**0.003**	**0.49**						
General		**6.8(4.6)**	**3.7(2.9)**	**4.9**	**<0.001**	**0.82**						
Total SOPS		**29.9(11.6)**	**24.5(9.9)**	**3.0**	**0.003**	**0.50**						
		Mean(SD)	**Mean(SD)**	**z**	**p**		**z***	**p***	**z****	**p****	**z*****	**p*****
ADHD inattention symptoms		**6.1(2.9)**	**3.4(2.8)**	**5.4**	**<0.001**	**0.95**	**4.8**	**<0.001**	**4.2**	**<0.001**	**3.3**	**0.001**
ADHD hyperactivity- impulsivity symptoms		**3.6(2.8)**	**2.2(2.4)**	**2.9**	**0.004**	**0.54**	1.7	0.10	0.2	0.87	0.7	0.50
ADHD total symptoms		**9.1(4.8)**	**5.6(4.6)**	**4.3**	**<0.001**	**0.75**	**3.7**	**<0.001**	**2.3**	**0.02**	**2.0**	**0.05**

Abbreviations: 22q PS+= 22q11.2 DS and subthreshold psychosis, ND PS+= Non-deleted subthreshold psychosis, ADHD-Attention Deficit Hyperactivity Disorder, WRAT4-Wide Range Achievement Test 4, SOPS= Scale of Prodromal Symptoms.

Notes: Statistically significant variables are highlighted in bold. *regressing out WRAT4 and age **regressing out age, WRAT4 and executive ***regressing out age, WRAT4, executive and total SOPS (excluding item D3 – significant attentional impairments).

Table 3. Comparisons of ADHD symptomatology between individuals with 22q11.2DS and individuals without the deletion with family history of psychosis.

Variable		**22q11.2DS (n=137)**	**Family history of psychosis (n=31)**									
		Mean(SD)/range	**Mean(SD)/range**	**χ^2, z**	**p**	**Cohen's d**						
Age		**14.0(4.5)/8 to 23**	**17.0(2.3)/11-23**	**-13.8**	**<0.001**	**-0.72**						
WRAT4		**-0.36(1.0)/-2.6-1.4**	**0.50(0.8)/-1.0-1.8**	**-3.2**	**0.002**	**-0.89**						
Executive		**-0.75(1.1)/-3.5-0.9**	**0.75(0.4)/-0.1-1.4**	**-5.2**	**<0.001**	**-1.49**						
		Mean(SD)	**Mean(SD)**	**χ^2, z**	**p**	**Cohen's d**						
Estimated household income ($)		**70617(29710)**	**41032(20449)**	**32.5**	**<0.001**	**1.05**						
Maternal education level		**15.0(2.4)**	**13.3(2.3)**	**12.5**	**<0.001**	**0.71**						
		N(%)	**N(%)**	**χ^2**	**p**							
Gender (males)(%)		72(53)	14(45)	0.6	0.50	0.12						
Race	**Caucasian**	**118(86)**	**9(29)**									
	African-American	**12(9)**	**18(58)**									
	Mixed	**2(2)**	**0(0)**									
	Asian	**5(3)**	**4(13)**	**49.8**	**<0.001**	**-1.12**						
ADHD diagnosis		**65(49)**	**3(10)**	**15.7**	**<0.001**	**0.64**						
		Mean(SD)	**Mean(SD)**									
SOPS	**Positive**	**5.7(6.3)**	**7.9(6.3)**	**-2.0**	**0.04**	**-0.35**						
	Negative	**9.5(7.8)**	**6.4(6.4)**	**2.8**	**0.005**	**0.41**						
	Disorganized	5.2(5.3)	3.7(3.8)	1.8	0.07	0.30						
	General	**6.1(6.0)**	**3.4(3.6)**	**2.9**	**0.004**	**0.48**						
	Total	26.5(22.7)	21.4(16.5)	1.22	0.22	0.24						
		Mean(SD)	**Mean(SD)**	**z**	**p**		**z***	**p***	**z****	**p****	**z*****	**p*****
ADHD inattention symptoms		**5.4(3.2)**	**2.7(2.8)**	**4.1**	**<0.001**	**0.86**	**4.8**	**<0.001**	**4.18**	**<0.001**	**2.34**	**0.02**
ADHD hyperactivity -impulsivity symptoms		**3.0(2.8)**	**1.2(1.9)**	**3.3**	**<0.001**	**0.68**	1.7	0.10	0.17	0.87	1.23	0.22
ADHD total symptoms		**7.9(5.1)**	**3.9(4.0)**	**4.0**	**<0.001**	**0.81**	**3.7**	**<0.001**	**2.31**	**0.02**	**2.03**	**0.04**

Abbreviations: ADHD-Attention Deficit Hyperactivity Disorder, WRAT4- Wide Range Achievement Test 4.*regressing out WRAT4 and age **regressing out age, WRAT4 and executive ***regressing out age, WRAT4, executive and total SOPS(excluding item D3 – significant attentional impairments). Psychosis = all non-schizophrenia psychotic disorders and mood disorders with psychotic features.