Running title: *Psychotic symptoms in the MTA*

Psychotic symptoms in ADHD: an analysis of the MTA database

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Abstract

Objective: To assess the prevalence of psychotic symptoms among youths (age 14-25 years) with a childhood diagnosis of attention-deficit/hyperactivity disorder (ADHD) combined type. **Method:** The participants in the Multimodal Treatment Study of Children with ADHD (MTA) and a local normative comparison group (LNCG) were systematically assessed 6, 8, 10, 12, 14, and 16 years after the original enrollment at a mean age of 8.5 years. Trained research assistants administered a psychosis screener, and positive screens were referred to study clinicians to confirm or exclude psychosis. Possible associations between screening positive and alcohol or substance use were assessed. **Results:** Data were available from 509 MTA participants (88% of the original MTA sample) and 276 LNCG subjects (96% of the original sample), with a mean age of 25.1 and 24.6 years, respectively, at Year 16. Twenty-six MTA subjects (5%, 95% CI: 3, 7) and 11 LNCG (4%, 95% CI: 2, 6) screened positive for at least one psychotic symptom ($p=0.60$). Most psychotic symptoms were transient. The prevalence of clinician-confirmed psychotic symptoms was 1.1% (95% C.I. 0.2, 2.1) in the MTA and 0.7% (0, 1.7) in the LNCG ($p=0.72$). Greater cannabis use was reported by those who screened ($p<0.05$) and were confirmed positive ($p<0.01$). **Conclusions:** There was no evidence that ADHD increased the risk for psychotic symptoms. In both the ADHD and normative comparison groups, more frequent cannabis use was associated with greater likelihood of experiencing psychotic symptoms, thus supporting the recommendation that youth should not use cannabis.

Introduction

Attention deficit/hyperactivity disorder (ADHD) is a common disorder of childhood that tends to persist into adolescence and adulthood. Psychotic disorders are rare before puberty, but their incidence increases in adolescence and peaks in early adult life. Schizophrenia, which has a population life-time morbidity risk of 0.7%, has onset in the second or third decade of life, and early onset schizophrenia, defined as onset before 18 years of age, accounts for about one-fourth of the cases.[1] Schizophrenia is typically preceded by functional impairments and developmental delays,[2] and ADHD symptoms are often part of the prodrome of psychosis.[3-4]

While the prevalence of psychotic disorders is low, isolated psychotic experiences are relatively common during development. A 3.7% prevalence of hallucinations and/or delusions was recently reported in a community sample of 7,054 youths aged 11-21 years.[5] A 7% prevalence of psychotic experiences was found in an epidemiological sample of 1,112 adolescents aged 13-16 years.[6] Sub-threshold symptoms, such as unusual thoughts and auditory misperceptions (illusions), are even more common, with rates as high as 12% in youth.[5]

Psychotic symptoms are diagnostically non-specific and can be found in the context of conditions other than schizophrenia, such as major depression, mania, substance abuse, seizure disorders, and other neurological disturbances.[7] Population-based epidemiological surveys indicate that the mean life-time prevalence of psychotic experiences in non-clinically referred general population is about 6%.[8] These psychotic symptoms have little psychopathological meaning unless they are severe or persistent.[9,10]

The association between ADHD symptoms and psychosis has been mainly studied by retrospective assessments of adults diagnosed with a psychotic disorder. A study of 122 adult patients with first-episode schizophrenia-spectrum disorders reported an ADHD prevalence of 17%.[11] Few data are available on the rate of psychosis in ADHD samples. A 10-year prospective case-control study of 140 children with ADHD and 120 matched controls did not find a difference in the rate of psychosis.[12] One case of psychotic disorder was found in a systematic follow-up of 135 men, mean age of 41 years, who were diagnosed with ADHD in childhood.[13] However, another study, which followed 208 children with ADHD up to a mean age of 31.1 years, found a 3.8% incidence of schizophrenia, representing a significant increase over the general population rate of 0.7%.[14] An increased risk for schizophrenia and bipolar among relatives of people with ADHD was also reported.[15]

We report here on the results of a 10-year prospective screening for psychotic symptoms conducted on a large cohort of individuals first diagnosed as children with ADHD combined type and a normative comparison group.[16.17] As part of the systematic follow-up assessments of the participants in the Multimodal Treatment Study of Children with ADHD (MTA), a screener for possible psychotic symptoms was periodically administered over a 10-year period (year 6 to year 6 after baseline) up to a mean age of 25 years. In parallel, a local normative comparison group (LNCG) received the same assessments. These data were analyzed to examine whether psychotic symptoms occurred more frequently in the MTA sample compared to the LNCG. In addition, possible associations of positive psychosis screening with substance abuse, IQ and parental mental illness, which had previously been found to be risk factors for psychotic experience in the general population,[18, 19] were also assessed.

Methods

Design

This was a systematic follow-up of the subjects who participated in the Multimodal Treatment Study of Children with ADHD (MTA), whose design and results have been extensively reported.[16, 20] At the end of the 14-month clinical trial, participants were naturalistically treated in the community and eligible for periodic follow-up assessments to evaluate mental health and other domains of functioning.

Sample

The MTA sample has been described in detail in previous publications.[16] Briefly, it consisted of 579 children, between 7.0 and 9.9 years of age (mean±SD: 8.5±0.8 years), 80% male, 61% white, 20% African American, and 8% Hispanic, meeting DSM-IV criteria for ADHD-combined type, who were randomized to receive pharmacotherapy with stimulant medication, behavior therapy, their combination, or community care, for 14 months, and afterwards were treated naturalistically and periodically reassessed for the following 15 years.[17,21,22] Among the exclusion criteria for MTA participation (as assessed at age 7-9 years), were: IQ below 80, DSM-IV diagnosis of bipolar disorder, psychosis, impairing OCD, or Tourette's syndrome, use of neuroleptic medication in previous 6 months, suicidal or homicidal behavior, and major neurological or medical illness. A local normative comparison group (LNCG) was added to the follow-up study, consisting of 289 subjects randomly selected from the same schools and grades, with the same sex proportion as the MTA patients and with the same inclusion/exclusion criteria except for ADHD diagnosis. At baseline, the LNCG received a comprehensive assessment battery, which included also the Diagnostic Interview Schedule for Children-Version IV and teacher-reported ratings of ADHD.[22] LNCG children were not excluded for having symptoms of ADHD. However, sensitivity analyses were conducted after excluding 27 LNCG children who met diagnostic criteria for ADHD.

Assessments

Psychotic symptoms were assessed at six time points: 6, 8, 10, 12, 14, and 16 years after the original MTA study entry. At each assessment point, trained research assistants interviewed and rated the subjects for possible psychotic symptoms using the Psychosis Screener and Follow-Up Diagnostic Impression (see Supplemental Appendix). Raters were not blind to subject status (i.e., MTA or LNCG). Subjects were asked about having experienced perceptions suggestive of auditory, visual, or somatic/tactile hallucinations, and assessed for possible unusual ideas or thoughts suggestive of delusional thinking. The screening for somatic/tactile hallucinations started with the Year 12 assessment. As part of the interview, subjects were assessed for disorganized speech and unusual or bizarre behavior, and for possible negative symptoms of psychosis, including flat affect, social withdrawal, and poverty of thoughts. The raters were trained to be broadly inclusive. Experiences and signs that could not be explained otherwise were considered possibly psychotic.

Positive psychotic symptoms (i.e., auditory, visual, and somatic/tactile hallucinations and delusions) were each scored by the rater as 1 (absent), 2 (possibly present but not psychotic), 3 (probably present and psychotic), or 4 (definitively present and psychotic). Negative psychotic symptoms (i.e., disorganized speech or appearance, inappropriate and flat affect, and social withdrawal) were rated as 1 (absent), 2 (mild, e.g., minimal emotional expression), 3 (moderate, e.g., monotone speech, poor eye contact), or 4 (severe, e.g., no emotional expression, no connection with interviewer). Subjects with a screening rating score of 3 or above on any of the positive symptoms, or of 4 on any of the negative symptoms were considered positive at the screening, and referred to the study clinician (a child psychiatrist or psychologist). Following review by the clinician, as spurious and not pathological, pathological but not psychotic, or possibly psychotic or psychotic.

The Substance Use Questionnaire (SUQ)[22,23] was administered at all assessments, beginning with the 2-year follow-up. It asked the subjects about frequency of use of alcohol and other substances (e.g., marijuana, inhalants) within the past 6 months (at the 2 to 10 year follow-up) and within the past 12 months (at the 12 to 16 year follow-up). Responses were recoded to estimated number of times alcohol, marijuana, or another substance, respectively, was used in 12 months, and, for each subject, the average times of use across all the assessment points was computed and used for the analyses. For nicotine, the subjects were asked to indicate use of cigarettes or other forms of tobacco in the past month at the 2 to 10 year follow-up assessments, and in the past 12 months at the 12 to 16 year follow-up assessments. For each assessment point, use was scored as 0 (did not use at all), 1 (used less than daily) and 2 (used daily), and for each subject, the average score across all assessments was computed and analyzed.

In parallel, starting with Year 12, participants self-reported health issues in the previous 2 years, including having received a psychiatric diagnosis, such as schizophrenia, schizoaffective disorder, major depression, and bipolar disorder.

The data were collected between 2002 and 2012 at the following clinical sites: University of California, Berkley/University of California; Duke University Medical Center; University of California, Irvine; Long Island Jewish Medical Center and New York University; McGill University/Montreal Children's Hospital; University of Pittsburgh; and Columbia University/New York State Psychiatric Institute and Mount Sinai Medical Center, New York.

Data analyses

Standard descriptive statistics were applied to the data. Group differences were tested with non-parametric or parametric tests, as appropriate and specified in the Results section, with statistical

significance accepted at two-tail $p<0.05$ without correction for multiple tests in these secondary analyses.

Results

Psychotic Symptom Screening in ADHD Subjects vs. Normative Group

Data were available from 509 MTA participants (87.5% of the originally enrolled MTA sample) and 276 LNCG subjects (95.5% of the original sample). The subjects who were retained were compared to those lost to follow-up. In the MTA, the non-retained group (n=70) had a statistically significant higher proportion of males, lower IQ, and lower family income than the retained group, but there were no differences in race or history of parental mental illness. In the LNCG, the non-retained group (n=13) had lower family income than the retained group, but di not differ with respect to sex, race, IQ, or history of parental mental illness. Among the retained subjects, the MTA differed from the LNCG by younger age, lower IQ, and history of parental mental illness (Table 1).

The number of subjects at each assessment point ranged from 290 to 436 in the MTA group, and from 191 to 252 in the LNCG (Table S1). The mean number of follow-up assessments per subject during the 10-year period was 4.7 $\pm$ SD 1.5 (median= 5) in the MTA and 5.2 $\pm$ 1.2 (median=6) in the LNCG ($t=4.79$, $df=786$, $p<0.0001$). During the 10-year period of observation, 26 MTA subjects (5%, 95% C.I. 3, 7) and 11 LNCG (4%, 95% C.I. 2, 6) screened positive for at least one psychotic symptom (Fisher's exact test, $p=0.6$; Table 2).

The rates of positive screens did not significantly differ between MTA and LNCG when the subgroups with the same number of visits were compared. Among subjects who had at least 4 assessments, the rate of positive screening was 5.5% in the MTA (n=405) and 4.4% in the LCNG (n=251)

(Fisher's exact test, p=0.59). The results of no statistically significant difference between MTA and LNCG did not change when sensitivity analyses were conducted excluding the n=27 LNCG with diagnosable ADHD (4.0%, 95% C.I. 1.5-6.4) (Supplemental Table 3).

Of the 26 MTA participants who screened positive, 8 had originally been randomized to combined treatment, 7 to medication management only, 4 to behavior therapy, and 7 to community comparison. The difference in the rate of positive screening by the original treatment group was not statistically significant.

Of the 37 subjects who screened positive, 36 had more than one biennial assessment. Among these 36, a positive screen occurred in more than one assessment for 8 subjects (21.6% of the cases), while the remaining 29 (78.4% of cases) screened positive only once.

Delusions, alone or accompanied by another psychotic symptom, accounted for positive screening for 55.6% (N=20) of the positive screens. Auditory hallucinations, alone or with other symptoms, accounted for 45.9% (N=17) of the positive screens (Supplemental Table 2). Negative symptoms of psychosis (social isolation and withdrawal) accounted for only one positive screening.

Screening positive was not associated with sex, ethnicity (Caucasian vs. other), or lower IQ. Positive-screened subjects were more likely to have a mother with history of mental health problems than the negative screens (Table 3).

The 37 subjects who screened positive were referred to the study clinician for further evaluation. However, this evaluation was missing for 7 subjects (4 MTA and 3 LNCG). Among the 26 MTA positive screens, psychosis was confirmed in 6 cases and ruled out in 16, while 4 had missing clinical evaluation. Among the 11 LNCG positive screens, psychosis was confirmed in 2 cases and excluded in 6, while 3 had missing clinical evaluation. The rate of confirmed psychosis (while

considering the missing cases "not confirmed") did not differ significantly between the MTA (1.1%, 95% CI: 0.2, 2.1) and LNCG (0.7%, 95% CI: 0.3-1.7) (Fisher exact test: 0.5, NS). If the cases with missing evaluation are considered as "psychosis not excluded", the rate of psychosis confirmed or not excluded was 1.9% (95% CI: 0.6, 2.9) in the MTA and 1.8% (95% CI: 0.2, 3.4) in the LNCG (Fisher exact test: 1.0, NS) (Table 2).

The original MTA treatment assignment of the 9 subjects with confirmed or not excluded psychosis was: combined treatment for 3 cases, medication management for 2, and community control for the remaining 4 subjects.

Upon administration of the health survey at assessment Years 12, 14, and 16, a community diagnosis of schizophrenia or schizoaffective disorder was reported by 3 of the MTA subjects (0.4%, 95% CI: 0.2, 0.95) and 2 of the LNCG subjects (0.7%, 95% CI: 0.3, 1.7). These 5 subjects were also positive at the psychosis screening (2 had clinician's review and were confirmed psychotic, while the other 3 had missing clinician review). No diagnosis of schizophrenia or schizoaffective disorder was reported by the subjects who were negative at the psychosis screening.

Psychotic Symptoms and Substances of Abuse

Screening positive for psychotic symptoms was associated with greater use of cannabis, but not of alcohol, nicotine, or other substances, in both the MTA and LNCG (Table 4 and Figure 1). Subjects whose psychotic symptoms were confirmed positive reported statistically significant greater use of cannabis and nicotine, but not of alcohol or other drugs, than the rest of the sample (Table 5). These results did not change when these analyses were repeated after excluding the n=27 LCNG subjects who were found to have diagnosable ADHD at the baseline assessment battery (Supplemental Tables 4 and

5). Nicotine and cannabis use were statistically significantly correlated in both the MTA (Spearman correlation coefficient rho=0.47, p<0.0001) and the LCNG (rho=0.59, p<0.0001) groups.

Discussion

This was a prospective study of youths diagnosed with ADHD combined type in childhood and periodically re-assessed up to a mean age of about 25 years. During a 10-year follow-up period (6 to 16 years after baseline), 5.1% percent of the ADHD subjects screened positive at least once for a self-reported psychotic experience. This rate was not statistically different from that found in a concurrently assessed local normative community sample, and is consistent with that reported in community samples of youths and adults.[5,19] These data indicate that a diagnosis of ADHD does not increase the risk of psychotic experiences or of psychotic disorder, a finding that is consistent with other follow-up studies of ADHD children into adulthood.[13, 24]

The major strength of this study is the consistent and repeated prospective assessments of psychosis for a large and well-defined cohort of children with ADHD-combined for 10 years, between 15 and 25 years of age, a period which is known to be the time of highest risk for developing psychotic disorders. The MTA sample was well characterized at entry, with exclusion of intellectual disability, autism, or other major psychopathology. Other strengths are the good sample retention (greater than 85%) over the years, and the concurrent assessment of a local normative comparison group.

Several important limitations must be considered. First, a diagnosis of bipolar or psychotic disorder or treatment with neuroleptic medication in the previous 6 months was reason for exclusion from the MTA at study screening when participants were 7 to 9 years of age. While none of the children who underwent formal screening for possible participation was excluded because meeting any of these criteria, we cannot exclude the possibility that referral sources, being aware of the entry criteria, might

not have referred children with psychosis. However, the LCNG was selected using the same criteria, thus attenuating the impact of possible biases. Second, the screening instrument used for this study antedates the development of detailed and probably more sensitive and specific instruments, such as the Structured Interview for Prodromal Syndromes, Comprehensive Assessment of At-Risk Mental States, or Prodromal Questionnaire, which are now used to assess psychosis in youth.[25,26] Third, although they were trained to collect data without bias, the raters who interviewed the MTA and LNCG subjects were not blind to their group status. Fourth, data for some clinical reviews following positive screening were missing from the database. As a way of addressing this deficiency, separate analyses considering these cases either non-confirmed or not excluded were conducted, without significant changes in the results. Finally, possible family history of psychosis was not part of the database. In support of the sensitivity of the methods used in this study, of those who were diagnosed with psychotic disorder in the community and reported it as adults, all were captured in our screening procedures, and none of those who screened negative reported a community diagnosis of psychotic disorder.

Delusions and auditory hallucinations were the most common type of psychotic symptom reported. The repeated, prospective, within-subject assessments showed that most psychotic experiences were transient. These findings are consistent with reports that psychotic experiences in the general population are usually transient and that only a small proportion of the 8-10% who experience them develop psychotic disorders.[10] Unlike studies in community samples,[5] we did not find that lower IQ or non-European ethnicity were risk factors for psychotic experiences. The MTA, however, excluded at entry children with IQ below 80.

The analyses reveal that more frequent use of cannabis, but not of alcohol or other drugs of abuse, is associated with a greater risk for screening positive and being confirmed positive for psychotic symptoms, in both the MTA and LNCG. This finding is consistent with other previous reports that

cannabis increases the risk for psychosis.[27-33] Specifically, it is the sustained, rather than sporadic, use of cannabis by adolescents that has been found to be associated with increased risk of subclinical psychotic symptoms, and especially paranoia.[29,30] The data from this study show that ADHD per se does not increase the risk for cannabis-associated psychotic symptoms.

Consistently with the well-known association between tobacco use and psychosis,[34] the analyses also found that the subjects who both screened and were confirmed positive had used nicotine more frequently than the other subjects. However, merely screening positive was not linked to nicotine use. Although the role of nicotine in psychosis is still a matter of debate,[35] the association of nicotine with psychosis is generally considered to reflect common risk factors rather than to be a causal effect.

In conclusion, in this sample of youths with childhood diagnosis of ADHD-combined type, the rate of psychotic symptoms through mean age 25 was not greater than that found in a normative comparison group, and was consistent with the epidemiologically expected rate of psychosis. Psychotic symptoms were transient phenomena in about three-fourth of the cases. The results confirm that sustained cannabis use is associated with an increased risk of psychotic experiences, thus supporting the recommendation that cannabis should not be used during development. These data also confirm that a diagnosis of ADHD does not increase the risk of psychotic experiences or of psychotic disorder.

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Disclaimer:

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References:

1. Owen MJ, Sawa A, Mortensen PB. Schizophrenia. Lancet. 2016;388(10039):86-97.
2. Cannon M, Caspi A, Moffitt TE, et al. Evidence for early-childhood, pan-developmental impairment specific to schizophreniform disorder: results from a longitudinal birth cohort. Arch Gen Psychiatry. 2002;59(5):449-56.
3. Rho A, Traicu A, Lepage M, Iyer SN, Malla A, Joober R. Clinical and functional implications of a history of childhood ADHD in first-episode psychosis. Schizophr Res. 2015 165(2-3):128-133.
4. Erlenmeyer-Kimling L, Rock D, Roberts SA, et al. Attention, memory, and motor skills as childhood predictors of schizophrenia-related psychoses: the New York High-Risk Project. Am J Psychiatry. 2000;157(9):1416-1422.
5. Calkins ME, Moore TM, Merikangas KR, et al. The psychosis spectrum in a young U.S. community sample: findings from the Philadelphia Neurodevelopmental Cohort. World Psychiatry. 2014;13:296-305.
6. Kelleher I, Corcoran P, Keeley H, et al. Psychotic symptoms and population risk for suicide attempt: a prospective cohort study. JAMA Psychiatry. 2013;70:940-948.
7. Hollis C. Schizophrenia and Allied Disorders. In: Rutter M, (eds). *Rutter's Child and Adolescent Psychiatry.* 5th edition. Malden, MA: Blackwell Publishing, 2008: pp. 737-758.
8. McGrath JJ, Saha S, Al-Hamzawi A, et al. Psychotic Experiences in the General Population: A Cross-National Analysis Based on 31,261 Respondents From 18 Countries. JAMA Psychiatry. 2015;72(7):697-705
9. Linscott RJ, van Os J. An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders. Psychol Med. 2013;43(6):1133-49.

10. Kaymaz N, Drukker M, Lieb R, et al. Do subthreshold psychotic experiences predict clinical outcomes in unselected non-help-seeking population-based samples? A systematic review and meta-analysis, enriched with new results. Psychol Med. 2012;42(11):2239-53.
11. Peralta V, de Jalón EG, Campos MS, Zandio M, Sanchez-Torres A, Cuesta MJ. The meaning of childhood attention-deficit hyperactivity symptoms in patients with a first-episode of schizophrenia-spectrum psychosis. Schizophr Res. 2011;126(1-3):28-35.
12. Biederman J, Monuteaux MC, Mick E, et al. Young adult outcome of attention deficit hyperactivity disorder: a controlled 10-year follow-up study. Psychol Med. 2006;36(2):167-79.
13. Klein RG, Mannuzza S, Olazagasti MA, et al. Clinical and functional outcome of childhood attention-deficit/hyperactivity disorder 33 years later. Arch Gen Psychiatry. 2012;69(12):1295-303.
14. Dalsgaard S, Mortensen PB, Frydenberg M, Maibing CM, Nordentoft M, Thomsen PH. Association between Attention-Deficit Hyperactivity Disorder in childhood and schizophrenia later in adulthood. Eur Psychiatry. 2014;29(4):259-263.
15. Larsson H, Rydén E, Boman M, Långström N, Lichtenstein P, Landén M. Risk of bipolar disorder and schizophrenia in relatives of people with attention-deficit hyperactivity disorder. Br J Psychiatry. 2013;203(2):103-106.
16. The MTA Cooperative Group: A 14-Month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder (ADHD). Arch Gen Psychiatry 1999;56:1073-1086.
17. Molina BSG, Hinshaw SP, Swanson JM, et al. The MTA at 8 years: prospective follow-up of children treated for combined type ADHD in a multisite study. J Am Acad Child Adolesc Psychiatry. 2009; 48(5):484-500.
18. Griffith-Lendering MF, Wigman JT, Prince van Leeuwen A, et al. Cannabis use and vulnerability for psychosis in early adolescence--a TRAILS study. Addiction. 2013;108:733-740.

19. Wiles NJ, Zammit S, Bebbington P, Singleton N, Meltzer H, Lewis G. Self-reported psychotic symptoms in the general population: results from the longitudinal study of the British National Psychiatric Morbidity Survey. Br J Psychiatry. 2006;188:519-526.
20. Arnold LE, Abikoff HB, Cantwell DP, et al. National Institute of Mental Health Collaborative Multimodal Treatment Study of Children with ADHD (the MTA). Design challenges and choices. Arch Gen Psychiatry. 1997;54:865-870.
21. Vitiello B, Elliott GR, Swanson JM, et al. Blood pressure and heart rate in the Multimodal Treatment of Attention Deficit/Hyperactivity Disorder Study over 10 years. Am J Psychiatry. 2012;169:167-177.
22. Molina BS, Hinshaw SP, Eugene Arnold L, et al. Adolescent substance use in the Multimodal Treatment Study of Attention-Deficit/Hyperactivity Disorder (ADHD) (MTA) as a function of childhood ADHD, random assignment to childhood treatments, and subsequent medication. J Am Acad Child Adolesc Psychiatry. 2013;52(3):250-263.
23. Molina BSG, Pelham WE. Childhood predictors of childhood substance use in a longitudinal study of children with ADHD. J Abnorm Psychol 2003;112:497-507.
24. Fischer M, Barkley RA, Smallish L, Fletcher K. Young adult follow-up of hyperactive children: self-reported psychiatric disorders, comorbidity, and the role of childhood conduct problems and teen CD. J Abnorm Child Psychol. 2002;30(5):463-75. Erratum in: J Abnorm Child Psychol. 2003 Oct;31:563.
25. Klein RG, Mannuzza S, Olazagasti MA, et al. Clinical and functional outcome of childhood attention-deficit/hyperactivity disorder 33 years later. Arch Gen Psychiatry. 2012;69(12):1295-303.

26. Miller TJ, McGlashan TH, Rosen JL, et al. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. Schizophr Bull. 2003;29:703-715.
27. Loewy RL, Therman S, Manninen M, Huttunen MO, Cannon TD. Prodromal psychosis screening in adolescent psychiatry clinics. Early Interv Psychiatry. 2012;6(1):69-75.
28. Moore TH, Zammit S, Lingford-Hughes A, et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet. 2007;370(9584):319-328.
29. Murray RM, Di Forti M. Cannabis and Psychosis: What Degree of Proof Do We Require? Biol Psychiatry. 2016;79(7):514-515
30. Bechtold J, Hipwell A, Lewis DA, Loeber R, Pardini D. Concurrent and sustained cumulative effects of adolescent marijuana use on subclinical psychotic symptoms. Am J Psychiatry. 2016;173(8):781-789.
31. Marconi A, Di Forti M, Lewis CM, Murray RM, Vassos E. Meta-analysis of the Association Between the Level of Cannabis Use and Risk of Psychosis. Schizophr Bull. 2016;42(5):1262-1269.
32. Volkow ND, Swanson JM, Evins E, et al. Effects of cannabis use on human behavior, including cognition, motivation, and psychosis: a review. JAMA Psychiatry. 2016;73:292-297.
33. Gage SH, Hickman M, Zammit S. Association between cannabis and psychosis: epidemiological evidende. Biol Psychiatry. 2016;79:549-556
34. Myles N, Newall HD, Curtis J, Nielssen O, Shiers D, Large M. Tobacco use before, at, and after first-episode psychosis: a systematic meta-analysis. J Clin Psychiatry. 2012;73:468-475.
35. Gurillo P, Jauhar S, Murray RM, MacCabe JH. Does tobacco use cause psychosis? Systematic review and meta-analysis. Lancet Psychiatry. 2015;2:718-725.

Table 1 – Study Sample

	MTA (n=509)	LNCG (n=276)	p
Age at Year 16 assessment, years, mean (SD)	25.12 (1.07)	24.58 (1.15)	<.0001
Male, n (%)	402 (80)	222 (79)	0.63
Caucasian, n (%)	283 (56)	138 (50)	0.13
IQ, mean (SD)	101.5 (14.7)	108.7 (19.1)	<.0001
Mother's mental illness history, n (%)[a]	101 (22)	37 (14)	0.01
Father's mental illness history, n (%)[b]	69 (18)	25 (11)	0.02

[a]MTA n=454 and LNCG n=261

[b]MTA n=394 and LNCG n=234

Table 2 – Psychotic Symptom Screening Outcome

	MTA (n=509)		LNCG (n=276)		p[c]
	N	% (95% C.I)	N	% (95% C.I)	
Screened positive at any of the assessment points	26	5.1 (3.1 – 7.0)	11	3.9 (1.6 – 6.2)	0.60
Psychosis was confirmed by further clinical review[a]	6	1.1 (0.2 – 2.1)	2	0.7 (0 -1.7)	0.72
Psychosis was confirmed or not ruled out[b]	10	1.9 (0.7 – 3.1)	5	1.8 (0.2 – 3.3)	1.00

[a]Clinical review was missing for 4 MTA and 3 LNCG subjects.

[b]Including the cases with confirmed psychosis and those with missing clinician review

[c]Fisher's exact test

Table 3 – Psychosis Symptom Screening and Sex, Ethnicity, IQ and Family Psychiatric History

	Screened positive	Screened negative	p[a]
	(n=37)	(n=831)	
Male n (%)	26 (70)	674 (81)	0.10
	(n=35)	(n=824)	
Caucasian n (%)	15 (57)	450 (45)	0.17
	(n=37)	(n=822)	
IQ, *Mean* (SD)	99.2 (15.7)	103.6 (16.7)	0.11
	(n=29)	(n=763)	
Biological Mother Mental Health Problems, yes n (%)	18 (36)	114 (19)	0.03
	(n=23)	(n=669)	
Biological Father Mental Health Problems, yes n (%)	5 (22)	93 (14)	0.28

[a]Chi-square or t-test

Table 4 – Psychotic Symptom Screening and Alcohol, Cannabis, Nicotine, and Other Drugs of Abuse in the MTA and LNCG

	MTA + (n=26)	MTA – (n=483)	LNCG + (n=11)	LNCG – (n=265)	P[b]
Alcohol, *Median* (IQR)[a]	17 (43)	19 (43)	9 (34)	21 (36)	0.93
Mean (SD), Range	64.4 (147.8) 0 - 730	37.3 (56) 0 - 677	56.6 (121.6) 0 - 415	31.4 (36.1) 0 - 230	
Marijuana, *Median* (IQR)	14 (179)	3 (122)	46 (147)	1 (40)	0.03[c]
Mean (SD) *Range*	108.7 (155.5) 0 - 437	84.1 (156.1) 0 - 1095	103.9 (148.4)[d] 0 - 489	46.3 (95.2) 0 - 489	
Nicotine, Median (IQR)	0.5 (1.4)	0.5 (1.1)	0.5 (1.0)	0.25 (0.8)	<0.001[d]
Mean (SD) *Range*	0.9 (0.9) 0 - 3	0.6 (0.6) 0 - 3	0.5 (0.5) 0 - 1.3	0.4 (0.5) 0 - 2.1	
Other drugs, *Median* (IQR)	0 (2)	0 (1)	0 (1)	0 (1)	0.79
Mean (SD) *Range*	23.3 (74.1) 0 – 366	10.7 (50.4) 0 – 547	10.4 (32.2) 0 – 107	3.8 (15.3), 0 – 156	

[a]IQR = Interquartile Rage (difference of its upper and lower quartiles)

[b] Kruskal-Wallis Test

[c]Statistically significant difference between positive and negative screens

[d]Statistically significant differences between the LNCG- and the MTA subgroups

Table 5 – Psychotic Symptom Screening and Alcohol, Cannabis, and Other Drug of Abuse

	Screened positive n=37	Screened negative n=748	p[a]		Confirmed positive n=8	All the others n=777	p[a]
Alcohol, *Median (IQR[b])* *Mean (SD)* *Range*	17 (47) 62.1 (138.9) 0-730	20 (40) 35.2 (49.9) 0-677	NS[c]		32 (99) 136 (248.2) 4-730	20 (40) 35.4 (51.6) 0-677	0.28
Marijuana, *Median (IQR)* *Mean (SD)* *Range*	20 (162) 107.3 (151.4) 0-487	3 (83) 70.7 (138.8) 0-1095	<0.05		175 (291) 222 (181.4) 6-489	2 (82) 70.9 (138.3) 0-1095	<0.001
Nicotine, *Median (IQR)* *Mean (SD)* *Range*	0.5 (1.3) 0.8 (0.8) 0-3	0.4 (1.0) 0.5 (0.6) 0-3	0.12		1.6 (0.6) 1.7 (0.4) 1.1-2.3	0.4 (1.0) 0.5 (0.6) 0-3	<0.0001
Other drugs, *Median (IQR)* *Mean (SD)* *Range*	0 (.2) 19.5 (64.3) 0-366	0 (1) 8.2 (41.6) 0-547	NS		0 (5) 47.9 (128.5) 0-366	0 (1) 8.4 (41.2) 0-547	0.42

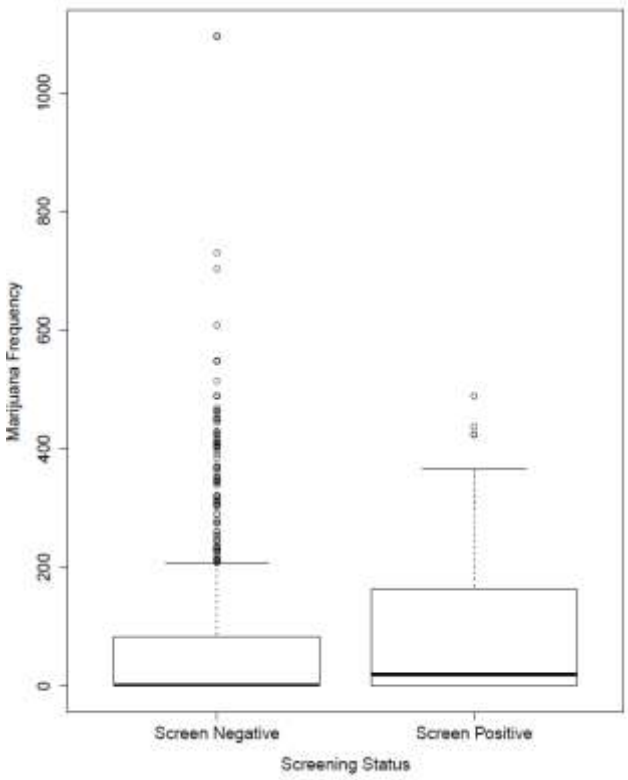
[a] Wilcoxon-Matt-Whitney test

[b] IQR = Interquartile Rage (difference between upper and lower quartiles)

Title and foot-note for Fig. 1 (next page)

Figure 1 – Frequency of cannabis use among the positive (n=37) and negative screens (n=748) for psychotic experiences[a]

[a]Frequency is expressed as the reported number of times that cannabis was used in past 12 months


Marijuana Frequency
0
200
400
600
800
1000
Screen Negative
Screen Positive
Screening Status

Supplemental Tab. 1: Screening for Hallucinations and Delusions

	Yr 6					**Yr 8**				**Yr 10**				**Yr 12**				**Yr 14**					**Yr 16**				
Score[a]	**1**	**2**	**3**	**4**	Total	**1**	**2**	**3**	Total	**1**	**2**	**3**	Total	**1**	**2**	**3**	Total	**1**	**2**	**3**	**4**	Total	1	2	3	4	Total
Auditory Hallucinations																											
MTA	276	10	4	0	290	400	19	3	422	396	11	3	410	402	9	3	414	420	13	2	1	436	402	10	3	2	417
LNCG	185	5	1	0	191	250	6	1	257	246	6	0	252	242	5	0	247	247	2	0	1	250	239	0	1	0	240
Visual Hallucinations																											
MTA	283	4	1	2	290	416	6	1	423	397	12	1	410	403	9	2	414	428	3	5	0	436	410	5	2	0	417
LNCG	186	5	0	0	191	254	2	1	257	249	3	0	252	246	1	0	247	246	4	0	0	250	239	1	0	0	240
Somatic Hallucinations[b]																											
MTA														406	7	1	414	427	6	3	0	436	407	7	3		417
LNCG														243	3	1	247	248	2	0	0	250	236	3	1		240
Delusions																											
MTA	271	15	3	0	289	409	13	0	422	393	14	3	410	399	13	1	413	425	9	2	0	436	402	11	3	1	417
LNCG	187	2	1	0	190	248	6	2	256	247	5	0	252	239	5	3	247	242	5	1	2	250	233	6	1	0	240

[a]Score:
1 = Symptom not present
2 = Symptom possibly present but not psychotic (e.g., hearing own voice inside the head, visual images of dead person, somatic sensations form medical disorder)
3 = Symptom probably present and psychotic
4 = Symptom definitely present

[b]Somatic hallucinations were added to the screening instrument only at Year 12.

Supplemental Table 2 - Reported Community Diagnoses for the Subjects who Screened positive

Initially screened positive for:	N	Psychosis was excluded by further clinical review		Psychosis was not excluded by further clinical review[a]	
		N	Reported diagnoses	N	Reported diagnoses
Auditory hallucinations only	6	6	none	0	n.a.
Auditory and visual hallucinations	1	1	major depression and personality disorder	0	n.a.
Auditory, visual and somatic hallucinations	2	1	none	1	schizoaffective
Auditory hallucinations and delusions	4	2	obsessive-compulsive disorder (1); none (1)	2	schizoaffective (2)
Auditory and visual hallucinations and delusions	1	1	none	0	n.a.
Auditory, visual and somatic hallucinations and delusions	2	0	n.a.	2	panic disorder (1); major depression (1)
Auditory hallucinations and social isolation	1	0	n.a.	1	none
Visual hallucinations	3	2	none (1); anxiety disorder NOS (1)	1	bipolar
Visual and somatic hallucinations	1	0	n.a.	1	alcohol abuse
Visual and delusions	1	1	none	0	n.a.
Somatic hallucinations	2	1	none	1	none
Delusions only	12	8	none (6); PTSD and cannabis and opiate abuse (1); generalized anxiety and mood disorder NOS	4	none (1); schizophrenia (1); schizoaffective disorder and OCD (1); cannabis abuse (1)

			(1)		
Social isolation	1	1	none	0	n.a.
Cumulative (any psychotic symptom)	**37**	**24**	**none (19); schizophrenia or schizoaffective disorder (0); other disorders (5)**	**13**	**none (3); schizophrenia or schizoaffective disorder (5);[b] bipolar (1); other disorders (4)**

n.a.: not applicable
OCD: obsessive compulsive disorder
NOS: not otherwise specified

[a]Including cases with confirmed or possible psychosis at clinician's review and cases for whom the clinician's review was missing
[b]Of the 5 subjects, 3 were MTA and 2 LNCG)

Supplemental Table 3 – Sensitivity Analysis: Psychotic Symptom Screening Outcome, After Excluding n=27 LNCG with Diagnosable ADHD

	MTA (n=509)		LNCG (n=249)		p[c]
	N	% (95% C.I)	N	% (95% C.I)	
Screened positive at any of the assessment points	26	5.1 (3.1 – 7.0)	10	4.0 (1.5 – 6.4)	0.59
Psychosis was confirmed by further clinical review[a]	6	1.1 (0.2 – 2.1)	1	0.4 (0.03 -1.1)	0.67
Psychosis was confirmed or not ruled out[b]	10	1.9 (0.7 – 3.1)	4	1.6 (0 – 3.1)	1.00

[a]Clinical review was missing for 4 MTA and 3 LNCG subjects.
[b]Including the cases with confirmed psychosis and those with missing clinician review
[c]Fisher's exact test

Supplemental Table 4 – Sensitivity Analysis: Psychotic Symptom Screening and Alcohol, Cannabis, and Other Drug of Abuse in the MTA and LNC, After Excluding n=27 LNCG with Diagnosable ADHD

	MTA + (n=26)	MTA – (n=483)	LNCG + (n=10)	LNCG – (n=239)	P[b]
Alcohol, *Median* (IQR)[a]	17 (43)	19 (43)	14(43)	21 (35)	0.94
Mean (SD), Range	64.4 (147.8) 0 - 730	37.3 (56) 0 - 677	61.6 (127.1) 0 - 415	30.1 (32.9) 0 – 229	
Marijuana, *Median* (IQR)	14 (179)	3 (122)	27 (120)	1 (33)	0.03[c]
Mean (SD) *Range*	108.7 (155.5), 0 - 437	84.1 (156.1), 0 - 1095	98.1 (155.1), 0 - 489	43.3 (93.1) 0 - 489	
Other drugs, *Median* (IQR)	0 (2)	0 (1)	0 (2)	0 (1)	0.61
Mean (SD) *Range*	23.3 (74.1) 0 – 366	10.7 (50.4) 0 – 547	11.4 (33.7) 0 – 107	3.1 (12.3), 0 – 156	

[a]IQR = Interquartile Rage (difference of its upper and lower quartiles)
[b] Kruskal-Wallis Test
[c]Statistically significant difference between positive and negative screens

Supplemental Table 5 – Sensitivity Analysis: Psychotic Symptom Screening and Alcohol, Cannabis, and Other Drug of Abuse, After Excluding n=27 LNCG with Diagnosable ADHD

	Screened positive n=36	Screened negative n=722	p[a]		Confirmed positive n=7	All the others n=751	p[a]
Alcohol, *Median (IQR[b])* *Mean (SD)* *Range*	17 (48) 63.6 (140.6) 0-730	20 (40) 35.1 (49.7) 0-677	0.76		53 (126) 154.4 (262.2) 4-730	20 (40) 35.4 (51.6) 0-677	N0.16
Marijuana, *Median (IQR)* *Mean (SD)* *Range*	14 (162) 105.8 (153.3) 0-489	2 (80) 70.6 (139.8) 0-1095	0.06		188 (322) 230.8 (194.2) 6-489	2 (80) 70.8 (139.2) 0-1095	0.002
Other drugs, *Median (IQR)* *Mean (SD)* *Range*	0 (2) 20 (65.2) 0-366	0 (1) 8.2 (41.9) 0-547	0.35		0 (9) 54.7 (137.2) 0-366	0 (1) 8.4 (41.6) 0-547	0.25

[a] Wilcoxon-Matt-Whitney test

[b] IQR = Interquartile Rage (difference between upper and lower quartiles)