Mental Health Service Use and Psychopharmacological **Treatment Following Psychotic Experiences** in Preadolescence

Martin Køster Rimvall, M.D., Jim van Os, Ph.D., Frank Verhulst, Ph.D., Rasmus Trap Wolf, M.Sc., Janne Tidselbak Larsen, M.Sc., Lars Clemmensen, Ph.D., Anne Mette Skovgaard, D.M.Sc., Charlotte Ulrikka Rask, Ph.D., Pia Jeppesen, Ph.D.

Objective: Psychotic experiences affect more than 10% of children and often co-occur with nonpsychotic mental disorders. However, longitudinal studies of the outcome of psychotic experiences based on unbiased information on mental health service use and psychotropic medications are scarce. The authors investigated whether psychotic experiences at ages 11-12 predicted a psychiatric diagnosis or treatment with psychotropic medications by ages 16-17.

Methods: In a longitudinal register-based follow-up study of the Copenhagen Child Cohort 2000, a total of 1,632 children ages 11-12 were assessed for psychotic experiences in faceto-face interviews. The children were also assessed for mental disorders and IQ. National registries provided information on perinatal and sociodemographic characteristics, on psychiatric disorders diagnosed at child and adolescent mental health services, and on prescribed psychotropic medications through ages 16-17.

Results: Among children who had not been previously diagnosed, and after adjustment for sociodemographic and perinatal adversities and IQ, psychotic experiences at ages 11–12 predicted receiving a psychiatric diagnosis in child and adolescent mental health services before ages 16-17 (adjusted hazard ratio=3.13, 95% CI=1.93, 5.07). The risk was increased if the child met criteria for a co-occurring mental disorder (not diagnosed in mental health settings) at baseline compared with no psychotic experiences or diagnosis at baseline (adjusted hazard ratio=7.85, 95% CI=3.94, 15.63), but having psychotic experiences alone still marked a significantly increased risk of later psychiatric diagnoses (adjusted hazard ratio=2.76, 95% CI=1.48, 5.13). Similar patterns were found for treatment with psychotropic medications.

Conclusions: Psychotic experiences in childhood predict mental health service use and use of psychotropic medications during adolescence. The study findings provide strong evidence that psychotic experiences in preadolescence index a transdiagnostic vulnerability for diagnosed psychopathology in adolescence.

Am J Psychiatry 2020; 177:318-326; doi: 10.1176/appi.ajp.2019.19070724

Psychosis can be viewed as a spectrum phenotype, ranging from extreme clinical manifestations in the form of psychotic disorders to psychotic experiences, including hallucinations, delusions, and thought disturbances, distributed across the general population and not conforming to a psychotic disorder (1). Psychotic experiences are common in childhood, with an estimated prevalence of around 17% among children ages 9-12 (2), and rates decrease to around 7% in adolescence and adulthood (1, 2). Psychotic experiences in childhood and preadolescence are associated with poorer overall functioning, in both children with and those without nonpsychotic mental disorders (3, 4).

Although childhood psychotic experiences are relatively common and may occur as transient phenomena within the range of normal development, they share genetic and environmental vulnerabilities with psychotic disorders (1, 5) and mark an increased risk of psychotic disorders later in life (6–8). Recent findings from a mainly adult population revealed that psychotic experiences predict later mental disorders transdiagnostically, particularly in the context of comorbid psychopathology and a family history of mental disorders (9). A recent meta-analysis showed that although psychotic experiences in childhood are strongly associated with nonpsychotic mental disorders in cross-sectional studies, longitudinal studies are scarce (6). Thus, there is little evidence that childhood psychotic experiences actually predict nonpsychotic mental disorders.

As shown in a recent review and meta-analysis, adults with psychotic experiences are approximately twice as likely to use mental health services compared with those without psychotic experiences (10). Studies examining the association between psychotic experiences and mental health service use or other

See related feature: Editorial by Mr. Healy and Dr. Cannon (p. 285)

help-seeking behaviors have mainly used a cross-sectional design or relied on self-reported help-seeking. However, in a 5-year follow-up study, individuals with psychotic experiences were more likely to seek mental health services over the follow-up period (11). In addition, in a similar 5-year follow-up study, Werbeloff and colleagues (12) found that psychotic experiences in young adulthood predicted increased risk for hospitalization for nonaffective psychotic disorders but not for nonpsychotic disorders. To our knowledge, no studies have explored the occurrence of childhood and adolescent psychotic experiences and use of mental health services prospectively. In addition, studies examining psychotic experiences in relation to psychopharmacological treatment are lacking.

In this birth cohort study, we examined the occurrence of psychotic experiences in children ages 11-12 and investigated whether psychotic experiences at that age would predict a psychiatric diagnosis in clinical settings or treatment with psychotropic medications. We also examined whether psychotic experiences would add to the prediction of a diagnosis or treatment with psychotropic medications in the context of co-occurring psychopathology or familial psychiatric vulnerability. We used independently assessed register-based data from mental health services and tested two hypotheses:

- 1. Among children from the general population without a past history of psychiatric contact, children with psychotic experiences at age 11 are more often diagnosed in mental health services or treated with psychotropic medication before ages 16-17 compared with children without psychotic experiences at age 11.
- 2. An increased risk of future diagnosis in mental health services or treatment with psychotropic medications will especially be found among children with psychotic experiences who also meet criteria for a psychiatric diagnosis at baseline or have a parent with a history of diagnosed mental disorder.

METHODS

Study Population

This study was a longitudinal register-based follow-up study of the Copenhagen Child Cohort 2000, a birth cohort encompassing 6,090 children from the general population born in 2000 (13). Baseline data for children in our study were obtained between May 2011 and October 2012 (at ages 11-12), and the children were followed up in registers until June 2017 (at ages 16-17). The total study population comprised 1,632 children (27% of the Copenhagen Child Cohort) who participated in face-to-face assessments at ages 11-12. Children who did not participate in the face-to-face assessment were characterized by lower birth weight and gestational age, as well as male sex, and they had younger and less educated mothers, higher probability of having immigrant parents, higher changes in family composition or rates of not living with both parents, and higher rates of parental mental illness. These findings have been described in detail elsewhere (14).

Child Assessments

Psychotic experiences. The psychosis screening section and supplement of the semistructured interview Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) (15) were used to assess psychotic experiences. The interview includes nine items on hallucinations and 13 items on delusions. A positive dichotomous rating required at least one rating of "likely" or "definitely" present. The measures of "lifetime before" and "last month" were collapsed, given a large overlap, as well as the assumption that a positive response reflects the same underlying vulnerability, regardless of the time of occurrence. In line with the K-SADS-PL guidelines, psychotic experiences were rated as not present if a verbal hallucination included only the child's name being called or if a delusion was hypothetical ("as if me and my best friend can read each other's thoughts") or culturally acceptable, for example, as part of shared religious beliefs. The interviews were performed by trained professionals under the supervision of a consultant child and adolescent psychiatrist who reviewed interview videos every 2 weeks. Interrater agreement for any psychotic experience was excellent (kappa=0.94) (4).

Mental disorders at age 11. Mental disorders were diagnosed according to ICD-10 research criteria on the basis of the Development and Well-Being Assessment (DAWBA) (16). The DAWBA is a highly structured comprehensive diagnostic interview, supplemented by open-ended questions, that includes information from parents, the child, and, in some cases, the child's teachers. Child and adolescent psychiatrists reviewed all available information in pairs and decided on final diagnoses. Disagreements were resolved by consensus diagnoses. Interrater agreement was good for any diagnosis (kappa=0.81), as detailed elsewhere (4). DAWBA-based diagnoses were made only for research purposes and were not communicated to the child or the parents.

IQ proxy. The block design test from the Wechsler Intelligence Scale for Children, 4th Edition (WAIS-IV), was used to assess general intelligence (17). The block design test is the single test that best correlates with full-scale WAIS IQ.

Register Data

ICD-10 hospital diagnoses. Date of diagnosis from all inpatient and outpatient contacts in nationwide public mental health services, from the child's birth in the year 2000 until the end of follow-up in June 2017, were obtained through the Danish National Patient Register (18). Contacts with private child and adolescent psychiatrists or psychologists or private hospitals (the latter very rare) are not included in the Danish National Patient Register. We included all nonorganic mental disorders (e.g., ICD-10 codes F10-F99), as well as registered suicide attempts and self-injury (ICD-10 codes X60-X84). Given data protection laws and ethical considerations to prevent personally identifiable data, the effect of psychotic

experiences on later specific diagnoses could not be assessed because of the relative rarity of some outcomes and the resulting small cell sizes. Therefore, the main outcome was any mental disorder. We subsequently constructed three pragmatic diagnostic categories to partly disentangle this broad variable: neurodevelopmental (hyperactivity and inattention diagnoses, conduct disorders, autism spectrum disorders, and intellectual disability), emotional (depressive and anxiety disorders), and other (substance-related disorders, psychotic disorders, eating disorders, and personality disorders). For further details, see the online supplement.

The same register was used to assess family history of psychiatric disorders from 1995 to 2011.

Psychotropic medications. To obtain information on children who received psychopharmacological treatment, we linked data from the Register of Medicinal Product Statistics. The database includes all redeemed prescriptions of all psychotropic medications that are reimbursed through the National Health Service (19). We included central stimulants, antidepressants, antipsychotics, and melatonin (for details on included Anatomical Therapeutic Chemical Classification codes, see the online supplement). Additionally, data from the Register of Medicinal Product Statistics ensured registration of children who received psychotropic medications from child and adolescent psychiatrists in private practice and were not in contact with hospital-based psychiatric services.

Register-based covariates. The Danish Civil Registration System was used to identify and link the participants using personal identification numbers between registers (20). Data were linked to provide information on sociodemographic characteristics from the Integrated Database for Labor Market Research and birth characteristics from the Medical Birth Register (21, 22). We used a family adversities index (score range, 0-6; both parents born outside Denmark, parents not living together at the time of the child's birth, any change in family composition between 2000 and 2010, mother <21 years old at the time of the child's birth, <10 years of maternal education, and household income within the lowest quartile in 2009-2010) and a perinatal health index (score range, 0-5; birth weight <2,500 g, gestational age <37 weeks, Apgar score <7, nonsingleton birth, and any registered birth complication). These indices have been described in detail elsewhere (14).

Statistical Analysis

We used Cox proportional hazards regression models to compare outcomes among children with and without psychotic experiences regarding the first date of psychiatric diagnosis in mental health services and the use of psychotropic medications. Individual follow-up started on the date of examination for psychotic experiences, and hazard ratios and adjusted hazard ratios and 95% confidence intervals were calculated. Children who had already been diagnosed with a psychiatric disorder in a mental health setting before examination for psychotic experiences at age 11 or 12 were excluded from the analyses. Children were censored at the date of event (date of first diagnosis or prescription of psychotropics, depending on the analysis), the date of emigration, or the end of follow-up (June 2017). We stratified analyses by meeting criteria for DAWBA-based mental disorders at ages 11-12 and by parental psychiatric diagnosis. Unadjusted results were graphically presented using cumulative hazard plots that were smoothed with Epanechnikov kernel smoothing to ensure that individuals could not be identified in the plots. Further analyses were adjusted for sex, birth and sociodemographic characteristics, and estimated IQ. The proportional-hazards assumptions were tested comparing Cox-predicted curves and Kaplan-Meier observed curves using survival curves and Schoenfeld residuals after model fitting. All analyses were performed with Stata, version 14, with a two-sided significance level of 5%.

Ethics

The Copenhagen Child Cohort 2000 study was approved by the Danish Data Protection Agency. The local Committee on Health Research Ethics found the study to be non-notifiable. The principles of the Declaration of Helsinki were followed; informed consent was obtained from the participants and their families, and data were anonymized and used for research purposes only.

RESULTS

In the 2011-2012 assessments, a total of 172 (10.5%) of the 1,632 participating children ages 11-12 screened positive for psychotic experiences at baseline. Among all participants, 60 children (3.7%) were already clinically diagnosed with a psychiatric disorder in the patient register before baseline and were therefore excluded from further analyses. Their rate of psychotic experiences was not increased compared with the rate among children included in the analyses (Table 1). The remaining 1,572 youths were followed until the end of the follow-up period in June 2017, at ages 16-17, comprising a total of 8,184 person-years. During this time, 90 youths (5.7% of eligible children) were diagnosed with psychiatric disorders in clinical settings. Most diagnoses before baseline were within the group of neurodevelopmental disorders, whereas emotional disorders were more common during the follow-up period (Table 1).

In crude analyses, psychotic experiences predicted an approximately threefold increase in risk of being diagnosed with a psychiatric disorder in clinical psychiatric settings (hazard ratio=3.08, 95% CI=1.91, 4.95) (Table 2). Adjustment for sex, birth and sociodemographic characteristics, and estimated IQ affected the estimated hazard ratio minimally (adjusted hazard ratio=3.13, 95% CI=1.93, 5.07). In addition, adjustments did not markedly change the estimates in the subsequent analyses (Tables 2-3). Having psychotic experiences with a co-occurring DAWBA-based diagnosis at ages 11-12 was associated with a particularly increased risk of later

TABLE 1. Distribution of the study sample on key childhood predictor and outcome variables in a longitudinal Danish register-based follow-up study

	-	gnosis Before ion (N=60)		ignosis During Up (N=90)	All Participants (N=1,632)		
Variable	N	%	N	%	N	%	
Psychotic experiences	7	11.7	23	25.6	172	10.5	
Any DAWBA diagnosis ^a	40	67.9	27	30.0	224	13.8	
Register diagnoses							
Neurodevelopmental	53	88.3	48	53.3	101	6.2	
diagnosis							
Emotional diagnosis	21	35.0	57	63.3	78	4.8	
Other diagnosis	12	20	37	41.1	49	3.0	

^a Data on the Development and Well-Being Assessment (DAWBA) were missing for 10 participants.

diagnosis of psychiatric disorders, revealing a dose-response pattern (adjusted hazard ratio=7.85, 95% CI=3.94, 15.63). Having either psychotic experiences or a DAWBA-based diagnosis at ages 11-12 predicted a later clinically diagnosed psychiatric disorder in a grossly similar way (adjusted hazard ratio=2.76, 95% CI=1.48, 5.13, and adjusted hazard ratio=3.29, 95% CI=1.88, 5.77, respectively). The same pattern, although less pronounced, was found for parental history of mental disorder (Table 2). The unadjusted cumulative incidence rates during the follow-up period are shown in Figure 1.

Psychotic experiences predicted both emotional (hazard ratio=2.99, 95% CI=1.64, 5.47) and neurodevelopmental (hazard ratio=3.79, 95% CI=2.03, 7.06) disorders, whereas the hazard ratio for the remaining group of other disorders was markedly lower (hazard ratio=1.47, 95% CI=0.57, 3.78). A total of 15 individuals were diagnosed with a psychotic disorder during the follow-up period. However, the vast majority of these diagnoses were schizotypy or psychosis not otherwise specified, which are often used clinically as tentative or working diagnoses. This subgroup was too small to be examined separately given ethical considerations and regulations on the use of register data.

The same analyses, this time with psychotropic medications as the outcome, and excluding the 72 individuals with register-based psychiatric disorders or psychotropic treatment before baseline, are presented in Table 3. The same overall patterns were observed. Psychotic experiences were associated with an approximately threefold increase in risk of psychotropic treatment during the follow-up period (adjusted hazard ratio=2.70, 95% CI=1.46, 5.00). Having both a DAWBA-based diagnosis and psychotic experiences was most strongly associated with psychopharmacological treatment during the follow-up period (adjusted hazard ratio=9.87, 95% CI=4.47, 21.83). However, DAWBA-based diagnosis alone more strongly predicted psychopharmacological treatment compared with psychotic experiences alone (adjusted hazard ratio=4.91, 95% CI=2.61, 9.25, and adjusted hazard ratio=2.03, 95% CI=0.84, 4.95, respectively), although still with overlapping confidence intervals. For further details on outcomes of register psychiatric disorders and psychopharmacological treatment, see the online supplement.

Model control by Schoenfeld residuals revealed that the proportionality assumption in the analyses stratified for DAWBA-based diagnosis was violated, because children with both psychotic experiences and a DAWBA-based diagnosis were diagnosed shortly after examination, whereas the remaining children were comparably more often diagnosed toward the end of the follow-up period. Hence, the hazard ratios in these analyses should be interpreted as average hazards across the follow-up period and not proportional. There was also suggestive evidence that children with psychotic experiences alone were diagnosed later than those with DAWBA-based diagnosis alone (Figure 1), since the two groups were almost not mutually proportional according to the Schoenfeld residual (p=0.093).

DISCUSSION

Main Findings

This study is, to our knowledge, the first prospective study to examine psychotic experiences in children in relation to independently assessed outcomes regarding psychiatric diagnosis from both inpatient and outpatient mental health services, across different categories of psychiatric disorders, as well as the use of psychotropic medications. Children with psychotic experiences at age 11, without a past history of clinical psychiatric disorders, were three times more likely to be diagnosed in psychiatric services or to receive psychotropic medications within 5 years of follow-up compared with children without psychotic experiences. The increased risk of diagnosis and treatment was observed across main groups of psychiatric disorders. Children with both psychotic experiences and a DAWBA-based diagnosis at age 11 were the subgroup most likely to be diagnosed in psychiatric services during the follow-up period. It is noteworthy that a significantly increased risk of later psychiatric disorders was also observed among children with psychotic experiences who did not meet criteria for a DAWBA-based diagnosis at age 11. In addition, parental history of mental disorders appeared to co-contribute to more detrimental outcomes of psychotic experiences.

Methodological Considerations

These findings should be interpreted in light of some strengths as well as limitations of the study design. The

TABLE 2. Hazard ratio for diagnosis of a mental disorder over 5 years of follow-up of the presence or nonpresence of psychotic experiences at ages 11-12 in children with no prior register psychiatric diagnosis (N=1,572)^a

		Any Mental Disorder (N=90)			Model 1 ^b			Model 2 ^c		
Variable	N	Hazard Ratio	95% CI	р	Hazard Ratio	95% CI	р	Hazard Ratio	95% CI	р
No psychotic experiences Psychotic experiences	1,407 165	3.08	Reference 1.92, 4.95	<0.001	3.14	Reference 1.94, 5.09	<0.001	3.13	Reference 1.93, 5.07	<0.001
Stratification by DAWBA ICD-10 diagnosis at baseline ^d										
No psychotic experiences and no DAWBA ICD-10 diagnosis	1,260		Reference			Reference			Reference	
Psychotic experiences without DAWBA ICD-10 diagnosis	119	2.81	1.53, 5.17	0.001	2.78	1.49, 5.18	0.001	2.76	1.48, 5.13	0.001
DAWBA ICD-10 diagnosis without psychotic experiences	138	3.28	1.89, 5.69	<0.001	3.33	1.90, 5.81	<0.001	3.29	1.88, 5.77	<0.001
Psychotic experiences with DAWBA ICD-10 diagnosis	46	6.40	3.25, 12.62	<0.001	7.73	3.88, 15.37	<0.001	7.85	3.94, 15.63	<0.001
Stratification by parental history of register mental disorder from 1995 to 2011										
No psychotic experiences and no parental history of mental disorder	1,249		Reference			Reference			Reference	
Psychotic experiences without parental history of mental disorder	135	3.36	1.96, 5.74	<0.001	3.56	2.06, 6.13	<0.001	3.55	2.06, 6.12	<0.001
Parental history of mental disorder without psychotic experiences	158	2.41	1.36, 4.28	0.003	2.61	1.44, 4.73	0.002	2.63	1.45, 4.77	0.001
Psychotic experiences with parental history of mental disorder	30	4.44	1.77, 11.12	0.001	4.74	1.85, 12.11	0.001	4.67	1.83, 11.92	0.001

^a DAWBA=Development and Well-Being Assessment.

study's strengths include the nearly 100% follow-up rate, as a result of register-based outcomes, and all outcome variables were independent of children's examinations at ages 11-12. The registers also provided unbiased information on parental history of mental disorders, and we could account for mental disorders among children diagnosed before measurement of psychotic experiences. We had a strong measure of psychotic experiences, because all children were interviewed by trained clinicians at baseline.

Limitations of the study include the lower participation rate of children with perinatal and sociodemographic adversities in the face-to-face examinations of psychotic experiences. However, a previous study demonstrated that attrition was nondifferential regarding exposure to psychotic experiences (14). Additionally, our study relied solely on hospital-based inpatient and outpatient diagnoses. This was

partially remedied by supplementing with data on the use of psychotropic medications prescribed by child and adolescent psychiatrists in private practice. Still, children with emotional disorders, such as anxiety, who most often solely receive therapeutic or psychosocial interventions outside psychiatric settings, are not included in the registers that we used. It should also be noted that first-time neurodevelopmental disorders were frequently diagnosed during the follow-up period (ages 11-16), although diagnostic criteria for these disorders require that symptoms be present in early childhood. However, the study instead adds value in reflecting the helpseeking behavior leading to clinical diagnoses in real-life settings, in which the overall good validity of the register diagnoses has been demonstrated (23). Finally, because this study was population based, mental disorders were rare, which required grouping of specific diagnoses. Psychotic disorders in

^b Model 1 adjusted for sex, perinatal health index, and family adversity index (data are missing for 98 individuals).

^c Model 2 further adjusted for IQ (data are missing for two individuals).

^d Data were missing for nine individuals.

TABLE 3. Hazard ratio for prescribed psychopharmaceuticals over 5 years of follow-up of the presence or nonpresence of psychotic experiences at ages 11-12 in children with no prior register psychiatric diagnosis or psychopharmacological treatment (N=1,556)^a

		Any Psychopharmaceutical (N=58)		utical		Model 1 ^b		Model 2 ^c		
Variable	N	Hazard Ratio	95% CI	р	Hazard Ratio	95% CI	р	Hazard Ratio	95% CI	р
No psychotic experiences Psychotic experiences	1,394 162	2.85	Reference 1.56, 5.20	0.001	2.71	Reference 1.47, 5.00	0.001	2.70	Reference 1.46, 5.00	0.001
Stratification by DAWBA ICD-10 diagnosis at baseline ^d										
No psychotic experiences and no DAWBA ICD-10 diagnosis	1,256		Reference			Reference			Reference	
Psychotic experiences without DAWBA ICD-10 diagnosis	119	2.24	0.93, 5.40	0.072	2.06	0.85, 5.00	0.111	2.03	0.84, 4.95	0.118
DAWBA ICD-10 diagnosis without psychotic experiences	129	5.28	2.83, 9.86	<0.001	4.96	2.65, 9.29	<0.001	4.91	2.61, 9.25	<0.001
Psychotic experiences with DAWBA ICD-10 diagnosis	43	8.86	4.05, 19.38	<0.001	9.73	4.41, 21.48	<0.001	9.87	4.47, 21.83	<0.001
Stratification by parental history of register mental disorder from 1995 to 2011										
No psychotic experiences and no parental history of mental disorder	1,241		Reference			Reference			Reference	
Psychotic experiences without parental history of mental disorder	133	2.34	1.13, 3.4.85	<0.022	2.28	1.09, 4.76	0.028	2.27	1.09, 4.74	0.029
Parental history of mental disorder without psychotic experiences	153	1.60	0.71, 3.59	0.254	1.56	0.68, 3.57	0.292	1.57	0.69, 3.60	0.282
Psychotic experiences with parental history of mental disorder	29	6.44	2.53, 16.39	<0.001	6.06	2.31, 15.90	<0.001	6.01	2.29, 15.77	<0.001

^a DAWBA=Development and Well-Being Assessment.

particular were rare up to age 16. Hence, to adhere to ethical guidelines and to ensure that the participants' anonymity was preserved, we could not assess the specific outcome of psychotic disorders. Because most psychotic disorders in this study cohort will likely be diagnosed in the two decades after the present study's follow-up period (24), it is likely that future follow-up of the cohort will reveal increased specificity of psychotic experiences in predicting psychotic disorders in adults, in line with previous longitudinal research (8, 12).

Interpretation

Although psychotic experiences predicted clinical diagnoses made in mental health settings and use of psychotropic medications in the 5-year follow-up, psychotic experiences were not associated with diagnosed psychiatric disorders before ages 11-12. Conversely, a previous cross-sectional

study of the same cohort found that psychotic experiences were strongly associated with DAWBA-based mental disorders, particularly emotional disorders, at ages 11-12 (4). This finding can be interpreted from the view of psychotic experiences as a general marker of distress (25). Children who had already been diagnosed at an early age, predominantly with neurodevelopmental disorders, likely had been offered psychiatric and psychosocial interventions, which may have alleviated distress.

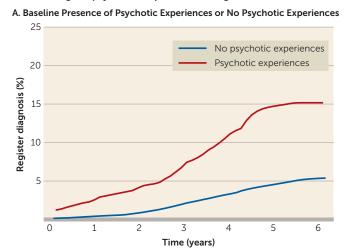
It is also noteworthy that adjusting for IQ and sociodemographic and perinatal adversities, which are known risk factors for later psychopathology, did not attenuate the estimated risk for later psychiatric disorder following psychotic experiences or a DAWBA-based diagnosis at ages 11-12. This finding can be interpreted in light of evidence from network models of psychopathology (26), suggesting that once

b Model 1 adjusted for sex, perinatal health index, and family adversity index (data were missing for 98 individuals).

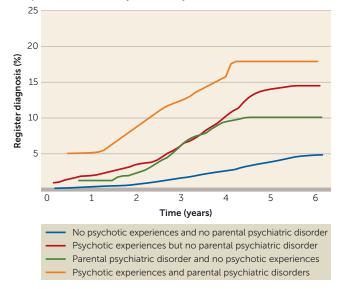
^c Model 2 further adjusted for IQ (data were missing for two individuals).

^d Data were missing for nine individuals.

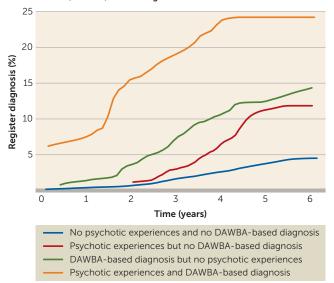
FIGURE 1. Smoothed cumulative hazard plots depicting the unadjusted cumulative incidence of register diagnosis of psychiatric disorder over a 5-year follow-up period after screening for psychotic experiences at ages 11-12







B. Baseline Presence of Psychotic Experiences or No Psychotic Experiences, Stratified by Baseline Development and Well-Being Assessment (DAWBA) Based Diagnosis



psychopathology has its onset, different symptoms reinforce each other in and by themselves (27) and over time cause more severe psychopathology.

Our study adds to the evidence that psychotic experiences in childhood are associated with later psychiatric disorders across the diagnostic spectrum, which according to a recent meta-analysis has not been convincingly shown in previous studies (6). Hence, our findings add to the evidence of psychotic experiences as an overall marker of the severity of general psychopathology (28). In addition, we incidentally found evidence suggesting a lagged effect on later clinical diagnosis in mental health services from only having psychotic experiences compared with only fulfilling criteria for DAWBA-based diagnosis at baseline. This suggests that psychotic experiences in childhood are not only a marker of contemporary distress but may also constitute an underlying vulnerability marker of psychopathology, which in turn opens a window of opportunity for early detection of clinically important psychopathology. However, this finding was not a result of our a priori hypotheses and requires replication.

Using a hard outcome of clinical diagnosis in mental health services, this study demonstrated effects of psychotic experiences in children on subsequent diagnosis in mental health services comparable to findings in adult populations in a recent meta-analysis (10). However, one must keep in mind that the absolute risk is relatively low: less than one in four of individuals with psychotic experiences who were not diagnosed within mental health services before baseline received a psychiatric diagnosis during the 5-year follow-up period. Low positive predictive values were also found in a recent study of adults using a broader psychoticism exposure variable (29). Nevertheless, our finding should be considered

in light of the fact that not all individuals in need of psychiatric treatment make contact with tertiary mental health services and that the positive predictive values in our study are expected to increase over later follow-up. Additionally, the children with psychotic experiences in our cohort who did not make contact with mental health services may still benefit from primary nonspecific prevention, such as psychological or psychosocial interventions in school settings or through social services. Importantly, the estimated hazard ratios reported for psychotic experiences alone and DAWBA-based diagnosis were similar, and the conjoined effects of psychotic experiences and meeting criteria for DAWBA-based diagnosis were striking (hazard ratios around 7-10 across models). This further supports the idea that psychotic experiences add to the prediction of future general mental health problems (30) and that these experiences contribute to the identification of children for whom secondary, or even tertiary, prevention is indeed indicated (31). Clinically, our findings support the general direction of preventive and early intervention services to provide transdiagnostic services and treatments (32, 33). Although previous studies have found that psychotic experiences show some degree of specificity for psychotic disorders (12, 34), there is a potential to prevent considerably higher numbers of common mental health outcomes (35).

This study adds to the existing evidence that psychotic experiences should be part of any mental health screening of children and adolescents (3, 4, 30). Even though psychotic experiences usually should not prompt imminent concern about development of a psychotic disorder, they should induce concern for the well-being of the child and lead to examination and identification of potential areas of intervention to reduce overall distress and burden (31). This in turn may ultimately lead to prevention and alleviation of mental health problems, and disorders for some individuals, across the diagnostic spectrum.

AUTHOR AND ARTICLE INFORMATION

Child and Adolescent Mental Health Center, Mental Health Services, Capital Region of Denmark (Rimvall, Verhulst, Wolf, Jeppesen); the Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen (Rimvall, Verhulst, Jeppesen); Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, the Netherlands (van Os); Department of Psychiatry and Psychology, Maastricht University Medical Center, Maastricht, the Netherlands (van Os); Department of Psychosis Studies, King's College London, King's Health Partners, Institute of Psychiatry, London (van Os); Department of Child Psychiatry/Psychology, Erasmus University Medical Center, Rotterdam, the Netherlands (Verhulst); Department of Public Health, Danish Center for Health Economics, University of Southern Denmark, Odense (Wolf); Lundbeck Foundation Initiative for Integrative Psychiatric Research, Center for Integrated Register-Based Research, and National Center for Register-Based Research, Aarhus University, Aarhus, Denmark (Larsen); Center for Telepsychiatry, Mental Health Services, Region of Southern Denmark, Odense (Clemmensen); National Institute of Public Health, University of Southern Denmark, Odense (Skovgaard); Department of Child and Adolescent Psychiatry, Research Unit, Aarhus University Hospital, Aarhus, Denmark (Rask); and Department of Clinical Medicine, Aarhus University, Aarhus, Denmark (Rask).

Send correspondence to Dr. Rimvall (martin.rimvall@regionh.dk).

Data collection for this Copenhagen Child Cohort 2000 project was supported by unrestricted grants from the Danish Foundations Tryg-Fonden (grant J. nr. 7-10-0189, 7-11-0341) and Lundbeckfonden (grant J. nr. R54-A5843).

The authors thank Anja Munkholm, Ph.D., Anne Dorothee Müller, M.Sc., and Maja Gregersen, M.Sc., for their contribution to the data collection.

Dr. Rimvall has received research grant funding from the Research Foundation of the Mental Health Services, Capital Region of Denmark. Dr. Verhulst publishes Dutch translations of the Achenbach System of Empirically Based Assessment, for which he receives remuneration. The other authors report no financial relationships with commercial interests.

Received July 13, 2019; revisions received September 10 and October 27, 2019; accepted November 12, 2019; published online Feb. 26, 2020.

REFERENCES

- 1. 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; 43:1133-1149
- 2. Kelleher I, Connor D, Clarke MC, et al: Prevalence of psychotic symptoms in childhood and adolescence: a systematic review and meta-analysis of population-based studies. Psychol Med 2012; 42: 1857-1863
- 3. Kelleher I, Wigman JTW, Harley M, et al: Psychotic experiences in the population: association with functioning and mental distress. Schizophr Res 2015; 165:9-14
- 4. Jeppesen P, Clemmensen L, Munkholm A, et al: Psychotic experiences co-occur with sleep problems, negative affect and mental disorders in preadolescence. J Child Psychol Psychiatry 2015; 56:
- 5. van Os J, Reininghaus U: Psychosis as a transdiagnostic and extended phenotype in the general population. World Psychiatry 2016; 15: 118-124
- 6. Healy C, Brannigan R, Dooley N, et al: Childhood and adolescent psychotic experiences and risk of mental disorder: a systematic review and meta-analysis. Psychol Med 2019; 49:1589-1599
- 7. Zammit S, Kounali D, Cannon M, et al: Psychotic experiences and psychotic disorders at age 18 in relation to psychotic experiences at age 12 in a longitudinal population-based cohort study. Am J Psychiatry 2013; 170:742-750
- 8. 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; 42:2239-2253
- 9. Kırlı U, Binbay T, Drukker M, et al: DSM outcomes of psychotic experiences and associated risk factors: 6-year follow-up study in a community-based sample. Psychol Med 2019; 49:1346-1356
- 10. Bhavsar V, McGuire P, MacCabe J, et al: A systematic review and meta-analysis of mental health service use in people who report psychotic experiences. Early Interv Psychiatry 2018; 12:275-285
- 11. Bhavsar V, Maccabe JH, Hatch SL, et al: Subclinical psychotic experiences and subsequent contact with mental health services. BJPsych Open 2017; 3:64-70
- 12. Werbeloff N, Drukker M, Dohrenwend BP, et al: Self-reported attenuated psychotic symptoms as forerunners of severe mental disorders later in life. Arch Gen Psychiatry 2012; 69:467-475
- 13. Olsen EM, Rask CU, Elberling H, et al: Cohort Profile: The Copenhagen Child Cohort Study (CCC2000). Int J Epidemiol (Epub ahead of print, December 26, 2019)
- 14. Jeppesen P, Larsen JT, Clemmensen L, et al: The CCC2000 Birth Cohort Study of Register-Based Family History of Mental Disorders and Psychotic Experiences in Offspring. Schizophr Bull 2015; 41: 1084-1094

- 15. Kaufman J, Birmaher B, Brent D, et al: Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 1997; 36:980-988
- 16. Goodman R, Ford T, Richards H, et al: The Development and Well-Being Assessment: description and initial validation of an integrated assessment of child and adolescent psychopathology. J Child Psychol Psychiatry 2000; 41:645-655
- 17. Wechsler D: WISC-IV Technical and Interpretive Manual. San Antonio, Tex, Psychological Corporation, 2003
- 18. Lynge E, Sandegaard JL, Rebolj M: The Danish National Patient Register. Scand J Public Health 2011; 39:30-33
- 19. Furu K, Wettermark B, Andersen M, et al: The Nordic countries as a cohort for pharmacoepidemiological research. Basic Clin Pharmacol Toxicol 2010; 106:86-94
- 20. Pedersen CB: The Danish Civil Registration System. Scand J Public Health 2011; 39:22-25
- 21. Petersson F, Baadsgaard M, Thygesen LC: Danish registers on personal labour market affiliation. Scand J Public Health 2011; 39:
- 22. Bliddal M, Broe A, Pottegård A, et al: The Danish Medical Birth Register. Eur J Epidemiol 2018; 33:27-36
- 23. Mors O, Perto GP, Mortensen PB: The Danish Psychiatric Central Research Register. Scand J Public Health 2011; 39:54-57
- 24. Jongsma HE, Gayer-Anderson C, Lasalvia A, et al: Treated incidence of psychotic disorders in the multinational EU-GEI study. JAMA Psychiatry 2018; 75:36-46
- 25. Myin-Germeys I, van Os J: Stress-reactivity in psychosis: evidence for an affective pathway to psychosis. Clin Psychol Rev 2007; 27: 409-424

- 26. Borsboom D, Cramer AO: Network analysis: an integrative approach to the structure of psychopathology. Annu Rev Clin Psychol 2013; 9:91-121
- 27. Wigman JTW, van Os J, Borsboom D, et al: Exploring the underlying structure of mental disorders: cross-diagnostic differences and similarities from a network perspective using both a top-down and a bottom-up approach. Psychol Med 2015; 45:2375-2387
- 28. Guloksuz S, van Nierop M, Lieb R, et al: Evidence that the presence of psychosis in non-psychotic disorder is environment-dependent and mediated by severity of non-psychotic psychopathology. Psychol Med 2015; 45:2389-2401
- 29. Livny A, Reichenberg A, Fruchter E, et al: A population-based longitudinal study of symptoms and signs before the onset of psychosis. Am J Psychiatry 2018; 175:351-358
- 30. Healy C, Gordon AA, Coughlan H, et al: Do childhood psychotic experiences improve the prediction of adolescent psychopathology? a longitudinal population-based study. Early Interv Psychiatry 2019; 13:1245-1251
- 31. Arango C, Díaz-Caneja CM, McGorry PD, et al: Preventive strategies for mental health. Lancet Psychiatry 2018; 5:591-604
- 32. McGorry PD, Hartmann JA, Spooner R, et al: Beyond the "at risk mental state" concept: transitioning to transdiagnostic psychiatry. World Psychiatry 2018; 17:133-142
- 33. van Os J, Guloksuz S, Vijn TW, et al: The evidence-based group-level symptom-reduction model as the organizing principle for mental health care: time for change? World Psychiatry 2019; 18:88-96
- 34. Kaymaz N, van Os J: Extended psychosis phenotype-yes: single continuum-unlikely. Psychol Med 2010; 40:1963-1966
- 35. Fusar-Poli P, Yung AR, McGorry P, et al: Lessons learned from the psychosis high-risk state: towards a general staging model of prodromal intervention. Psychol Med 2014; 44:17-24