ORIGINAL ARTICLE

Familial Predisposition for Psychiatric Disorder

Comparison of Subjects Treated for Cannabis-Induced Psychosis and Schizophrenia

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Context: Cannabis-induced psychosis is considered a distinct clinical entity in the existing psychiatric diagnostic systems. However, the validity of the diagnosis is uncertain.

Objectives: To establish rate ratios of developing cannabis-induced psychosis associated with predisposition to psychosis and other psychiatric disorders in a first-degree relative and to compare them with the corresponding rate ratios for developing schizophrenia spectrum disorders.

Design: A population-based cohort was retrieved from the Danish Psychiatric Central Register and linked with the Danish Civil Registration System. History of treatment of psychiatric disorder in family members was used as an indicator of predisposition to psychiatric disorder. Rate ratios of cannabis-induced psychosis and schizophrenia associated with predisposition to psychiatric disorders were compared using competing risk analyses.

Setting: Nationwide population-based sample of all individuals born in Denmark between January 1,1955, and July 1, 1990 (N = 2 276 309).

Patients: During the 21.9 million person-years of follow-up between 1994 and 2005, 609 individuals received treatment of a cannabis-induced psychosis and 6476 received treatment of a schizophrenia spectrum disorder.

Results: In general, the rate ratios of developing cannabis-induced psychosis and schizophrenia spectrum disorder associated with predisposition to schizophrenia spectrum disorder, other psychoses, and other psychiatric disorders in first-degree relatives were of similar magnitude. However, children with a mother with schizophrenia were at a 5-fold increased risk of developing schizophrenia and a 2.5-fold increased risk of developing cannabis-induced psychosis. The risk of a schizophrenia spectrum disorder following a cannabis-induced psychosis and the timing of onset were unrelated to familial predisposition.

Conclusions: Predisposition to both psychiatric disorders in general and psychotic disorders specifically contributes equally to the risk of later treatment because of schizophrenia and cannabis-induced psychoses. Cannabis-induced psychosis could be an early sign of schizophrenia rather than a distinct clinical entity.

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Both the *International Classification of Diseases, Tenth Revision* (*ICD-10*),[1] and the *DSM-IV*[2] include a cannabis-induced psychotic disorder diagnosis (sometimes called "cannabis psychosis"). Despite this, the diagnosis is controversial.[3] Few studies have investigated the condition, and it has proved difficult to establish a specific symptom profile or to delineate it from other psychotic conditions.[4-8] Other ways of validating the diagnosis such as follow-up or family studies are few. In the only existing follow-up study, we showed that almost 50% of the patients treated because of cannabis-induced psychosis in Denmark, with no history of psychosis, had a diagnosis of a schizophrenia spectrum disorder within a mean follow-up period of 5.9 years.[9] This documents that cannabis-induced psychoses and schizophrenia are closely associated; however, the role of genetic liability remains unclear. None of the existing studies of cannabis-induced psychosis systematically evaluated the potential role of familial predisposition; however, other studies have compared predisposition in patients with schizophrenia with and without concurrent cannabis use.[4,7,10] The results of these studies have been conflicting.

Whether cannabis-induced psychosis is a distinct clinical entity is unclear. The existing knowledge base does not enable a firm hypothesis about the validity of the

diagnosis. One way of investigating this subject is to evaluate data on familial predisposition to psychiatric disorders, and this was the purpose of the present study. First, we investigated whether cannabis-induced psychosis can be differentiated from schizophrenia on the basis of a history of psychiatric disorder in first-degree relatives. Second, we evaluated the absolute risk of having a diagnosis of schizophrenia spectrum disorder (F20, schizophrenia; F21, schizotypal disorder; and F25, schizoaffective disorders) after treatment of a cannabis-induced psychosis subdivided by familial predisposition to psychiatric disorders.

METHODS

STUDY POPULATION

The Danish Civil Registration System,[11] established in 1968, includes all persons alive and residing in Denmark. Among other variables, it includes information on Civil Registration System number, sex, date of birth, place of birth, and continuously updated information on vital status. The Civil Registration System number is used as a personal identifier in all national registers, enabling accurate linkage between registers. The study population included all persons born in Denmark between January 1, 1955, and July 1, 1990, and who were alive at their 15th birthday (N = 2 310 475).

ASSESSMENT OF PSYCHIATRIC DISORDERS

Throughout this article, the term "predisposition" refers to a history of psychiatric treatment in a first-degree family member. The study population and their parents and siblings were linked with the Danish Psychiatric Central Register,[12] which has been computerized since 1969. In Denmark, psychiatric treatment is free and there are no private psychiatric hospitals. Consequently, the Danish Psychiatric Central Register contains data on all admissions to Danish psychiatric inpatient facilities. Since 1995, information about outpatient visits to psychiatric departments has been included in the register. At present, it includes data on approximately 650 000 persons and 2.8 million psychiatric contacts (admission or outpatient visit). From 1969 to 1993, the diagnostic system used was the Danish modification of the *International Classification of Diseases, Eighth Revision* (*ICD-8*),[13] and from January 1, 1994, the diagnostic system used was the *ICD-10*.[1] Cohort members were classified as having cannabis-induced psychosis (*ICD-10* code F12.5), schizophrenia spectrum disorder (*ICD-10* codes F20, F21, or F25), schizophrenialike disorder (all remaining F2x diagnoses), manic episode (*ICD-10* code F30), bipolar affective disorder (*ICD-10* code F31), or other substance-induced psychosis (*ICD-10* code F1x.5 excluding F.12.5) if they had a diagnosis of the disorder in relation to any type of psychiatric treatment. For each disorder, the date of onset was defined as the first day of the first contact with the psychiatric treatment system.

Parents and siblings were classified hierarchically as having a history of schizophrenia spectrum disorder (*ICD-8* code 295; and *ICD-10* codes F20, F21, or F25), schizophrenialike disorder (*ICD-8* codes 297, 298.39, or 301.83; and *ICD-10* codes F2x, excluding F20, F21, and F25), other psychosis (*ICD-8* codes 292, 296, or 298, excluding 298.39, 299; and *ICD-10* codes F11.5, F13.5, F14.5, F15.5, F16.5, F17.5, F18.5, F19.5, F30, or F31), and other diagnosis (any remaining diagnosis).

In the Danish Psychiatric Central Register, information about cannabis-induced psychosis was first registered using the *ICD-10* classification (from 1994 onwards) whereas the information about the remaining disorders of interest was registered using both the *ICD-8* (1969-1993) and the *ICD-10* classification (from 1994 onwards). Therefore, the outcomes of interest were based on the *ICD-10* classification and the predispositions of interest were based on both classifications. The study was approved by the Danish Data Protection Agency.

STUDY DESIGN

Data were analyzed using competing risk survival analyses.[14] A total of 2 276 309 persons were followed up from their 15th birthday or January 1, 1994, whichever occurred later. Follow-up ended at the first of the following events: psychiatric contact with cannabis-induced psychosis, schizophrenia spectrum disorder, schizophrenialike disorder, manic episode, bipolar affective disorder, or other substance-induced psychosis; death; emigration from Denmark; or July 1, 2005. In the competing risk analyses, the outcomes of interest were cannabis-induced psychosis and schizophrenia spectrum disorder.

ESTIMATION OF RATE RATIOS ASSOCIATED WITH HEREDITARY PREDISPOSITION TO PSYCHOSES

The purpose of the first analysis was to evaluate the effect of hereditary predisposition for psychosis and other psychiatric disorders on the occurrence of cannabis-induced psychosis and the occurrence of schizophrenia spectrum disorder without a history of cannabis-induced psychosis. The rate ratio of developing cannabis-induced psychosis and schizophrenia spectrum disorder associated with predisposition to psychiatric disorders was estimated using log-linear competing risk Poisson regression.[14-16] For each outcome of interest, rate ratios were adjusted for age, calendar year, and its interaction with sex. Age, calendar year, and history of mental illness in a sibling were treated as time-dependent variables,[17] and all other variables were treated as variables independent of time. To reduce the risk of residual confounding, age was categorized as 15, 16, 17, 18, 19, 20 to 21, 22 to 23, 24 to 25, 26 to 27, 28 to 29, 30 to 34, 35 to 39, 40 to 44, and 45 or more completed years. Calendar year of diagnosis was categorized in 1-year age bands (1994-2005). *P* values were based on likelihood ratio tests, and 95% confidence intervals were calculated using the Wald test.[17]

ESTIMATION OF ABSOLUTE RISK ASSOCIATED WITH TREATMENT OF CANNABIS-INDUCED PSYCHOSIS AND HEREDITARY PREDISPOSITION TO PSYCHIATRIC DISORDERS

The second analysis estimated the absolute risk of developing a schizophrenia spectrum disorder after having received treatment of a cannabis-induced psychosis subdivided by the various familial predispositions to psychiatric disorders. We used the same follow-up period as in the first analysis except that follow-up started on the day of the first treatment of a cannabis-induced psychosis, a schizophrenia spectrum diagnosis was the outcome of interest, and time since the first treatment of a cannabis-induced psychosis was included in the model as a time-dependent variable. To increase power in these analyses, all persons who received treatment of a cannabis-induced psychosis were followed up (894 individuals) until the first diagnosis with schizophrenia spectrum disorder, if any, irrespective of other diagnoses made during follow-up. Because of the limited number of subjects, predispositions from family members were collapsed into 1 category; that is, schizophrenia, schizophrenia-

Table. Rate Ratios (95% Confidence Intervals) for Developing Schizophrenia Spectrum Disorder and Cannabis-Induced Psychosis Depending on Family History[a]

Diagnosis in Family Member	History in Father (*P*=.13)			History in Mother (*P*=.04)			History in Siblings (*P*=.38)		
	Schizophrenia Spectrum Disorder (n=6476)	Cannabis-Induced Psychosis (n=609)	*P* Value[b]	Schizophrenia Spectrum Disorder (n=6476)	Cannabis-Induced Psychosis (n=609)	*P* Value[b]	Schizophrenia Spectrum Disorder (n=6476)	Cannabis-Induced Psychosis (n=609)	*P* Value[b]
Schizophrenia spectrum disorder	3.58 (2.89-4.44)	4.51 (2.40-8.47)	.51	5.12 (4.40-5.94)	2.57 (1.32-5.00)	.03	4.16 (3.65-4.75)	2.72 (1.56-4.73)	.12
Schizophrenialike disorder	2.53 (2.02-3.17)	1.78 (0.74-4.30)	.42	2.76 (2.32-3.28)	3.45 (2.06-5.79)	.43	2.68 (2.13-3.36)	2.48 (1.10-5.55)	.85
Other psychosis	1.67 (1.40-1.99)	1.57 (0.84-2.93)	.84	1.92 (1.67-2.22)	2.62 (1.70-4.03)	.20	2.03 (1.53-2.70)	2.52 (1.04-6.10)	.66
Other diagnosis	1.71 (1.58-1.85)	2.28 (1.81-2.86)	.02	1.96 (1.83-2.11)	2.38 (1.92-2.96)	.10	1.79 (1.64-1.94)	2.09 (1.61-2.71)	.27
No psychiatric treatment	1 [Reference]	1 [Reference]		1 [Reference]	1 [Reference]		1 [Reference]	1 [Reference]	

[a] Data for 2.2 million persons born in Denmark between January 1, 1955, and July 1, 1990, and followed up between January 1, 1994, and July 1, 2005. All estimates were adjusted for age, sex, calendar period, place of birth, and the difference in age at onset between schizophrenia and cannabis-induced psychosis for each sex. Estimates were mutually adjusted for the different types of family history.

[b] *P* values are for rowwise comparisons for the different types of first-degree relatives (eg, rate ratio of receiving treatment for a schizophrenia spectrum disorder compared with a cannabis-induced psychosis if there is a treatment history for schizophrenia spectrum disorder in the father).

like disorder, other psychoses, and other diagnosis were included in any psychiatric disorder. In the Danish psychiatric treatment system, it is possible to receive diagnoses both in an acute-treatment ward, in which a patient can stay for a limited time, and at admission. If a patient had a diagnosis of a cannabis-induced psychosis initially and the diagnosis was changed to a schizophrenia spectrum disorder less than 2 days later, it was interpreted as an initial misclassification being corrected at admission, and the registration was excluded from further analysis.

The cumulative incidence of schizophrenia spectrum disorder after treatment of a cannabis-induced psychosis was estimated using competing risk Cox regression.[18] It measures the percentage of persons in the population who had developed schizophrenia spectrum psychoses at a given time, accounting for the fact that individuals may die or emigrate before the onset of schizophrenia spectrum disorder.

RESULTS

In this population-based cohort of 2.3 million persons born in Denmark between January 1, 1955, and July 1, 1990, and followed up during 21 868 315 person-years at risk from 1994 to 2005, a total of 609 individuals received treatment of a cannabis-induced psychosis and 6476 individuals received treatment of a schizophrenia spectrum disorder.

HEREDITARY PREDISPOSITION: CANNABIS-INDUCED PSYCHOSIS VS SCHIZOPHRENIA

The rate ratios and the corresponding confidence intervals for developing schizophrenia or cannabis-induced psychosis depending on predisposition to psychiatric disorders in first-degree relatives are given in the **Table**. For example, the risk of developing a schizophrenia spectrum disorder was increased 3.58-fold, and the risk of developing a cannabis-induced psychosis was 4.51-fold higher in children whose father had a schizophrenia spectrum disorder compared with those whose father did not. Predisposition to psychiatric disorder in mothers showed a main difference for all comparisons (*P*=.04) and a specifically lower rate ratio of having a diagnosis of a cannabis-induced psychosis compared with schizophrenia spectrum disorder if a mother had a schizophrenia spectrum disorder (*P*=.03). Predisposition to psychiatric disorders other than psychosis in fathers (*P*=.02) was also associated with increased risk of treatment of a cannabis-induced psychosis. The estimates were of similar magnitude for the remaining comparisons.

ABSOLUTE RISK OF SCHIZOPHRENIA AFTER TREATMENT OF A CANNABIS-INDUCED PSYCHOSIS

The absolute risk of schizophrenia in individuals treated because of a cannabis-induced psychosis was the focus of the next analysis. For each group of family history, the **Figure** shows the cumulative incidence of schizophrenia spectrum disorder as a function of time since treatment of a cannabis-induced psychosis. Approximately half of the subjects who received treatment of a cannabis-induced psychosis developed a schizophrenia spectrum disorder within 9 years after treatment. Furthermore, the risk of developing a schizophrenia spectrum disorder was virtually independent of familial predisposition, as evidenced by the high degree of overlap. The risk of having a diagnosis of schizophrenia spectrum disorder in the short term was slightly higher in subjects with predisposition from both parents, but this effect disappeared with time.

COMMENT

In terms of estimated rate ratios, persons who develop cannabis-induced psychosis are as predisposed to schizophrenia spectrum disorder and other psychiatric disorders as those who develop schizophrenia spectrum dis-

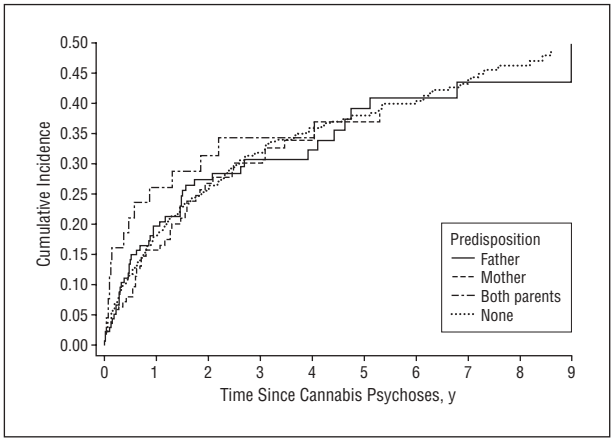

Figure. Cumulative incidence of schizophrenia spectrum disorder diagnoses in 894 individuals born in Denmark between January 1, 1955, and July 1, 1990, and treated because of cannabis-induced psychosis. Of these, 309 developed a schizophrenia spectrum disorder during follow-up between January 1, 1995, and July 1, 2005.

order without a history of cannabis-induced psychosis. Furthermore, a high percentage of patients who develop schizophrenia spectrum disorder after the cannabis-induced psychosis and the timing and rate of this outcome are independent of family history of psychiatric disorder.

IS CANNABIS-INDUCED PSYCHOSIS A DISTINCT DIAGNOSTIC ENTITY?

Several criteria can be used to evaluate the validity of psychiatric disorders. In a classic article, Robins and Guze[19] proposed that the following interacting phases should be used: clinical description, laboratory studies, delineation from other disorders, follow-up studies, and family studies. The present family study thus provides one approach to validate the diagnosis of cannabis-induced psychosis. In the following paragraphs, we briefly review what other studies have shown regarding the remaining criteria and discuss the findings outlined in the "Results" section in that context.

Despite much effort, it has been impossible to establish a symptom profile that consistently differentiates persons with cannabis-induced psychosis from those with other psychotic conditions.[3,5,6,20,21] The same is true for studies comparing persons with schizophrenia who have or have not been using cannabis.[4,8,10,22-24] Following the diagnostic criteria, clinicians, therefore, have the difficult task of determining whether a psychotic condition developed immediately after cannabis use. In addition, they have the often impossible task of judging whether the condition would have developed in the absence of cannabis use. Consequently, individuals who use cannabis or have access to the substance are at risk of having a diagnosis of cannabis-induced psychosis, although in reality they have schizophrenia.

To our knowledge, we have previously published the only follow-up study of subjects treated for cannabis-induced psychosis.[9] In this study, we found that approximately half of the subjects developed a schizophrenia spectrum disorder at some time after the cannabis-induced psychosis. All individuals with cannabis-induced psychosis should not be expected to have a diagnosis of schizophrenia spectrum disorder at a later time, even if cannabis-induced psychosis is an early manifestation of schizophrenia rather than a valid diagnosis. This is because not all of those who receive treatment of schizophrenia are readmitted. A study based on the same registers used in the present study found that 19% of those who had a diagnosis of schizophrenia were not readmitted after 10 years of follow-up.[25] The poor outcome for the patients and that the present study demonstrates that the risk of schizophrenia after a cannabis-induced psychosis is independent of familial predisposition further challenge the idea that cannabis-induced psychosis is a benign condition that can be clearly differentiated from schizophrenia.

Insofar as family studies, few existing data are available. Some studies have sporadically mentioned the presence of psychopathologic findings in relatives of subjects with cannabis-induced psychosis or patients with psychoses with cannabis-positive urine screening results, but no consistent pattern has appeared.[6-8,10,26-31] A recent study by Boydell et al[4] is particularly important. These authors studied the family history of schizophrenia in 757 patients who did or did not use cannabis with onset of schizophrenia and found no difference between the groups in the percentage of patients with a positive family history of schizophrenia. These findings are consistent with those of the present study.

The results of this study add new weight to the criticism of the diagnosis of cannabis-induced psychosis. If the rate ratio of hereditary predisposition had differed between persons who developed cannabis-induced psychosis and those who developed schizophrenia, it might have provided some indirect support for the validity of the diagnosis. However, it was found that it is impossible to differentiate between the 2 disorders on the basis of history of psychiatric disorder in first-degree relatives. Altogether, these findings, in addition to those of previous studies, indicate that cannabis-induced psychosis may not be a valid diagnosis but an early marker of schizophrenia. Replication of the results would further strengthen this assertion.

DOES CANNABIS CAUSE SCHIZOPHRENIA?

Cannabis use is associated with increased risk of schizophrenia.[32-34] Several longitudinal studies have suggested that this relationship could be causal.[35-42] However, the issue remains controversial, and some find the evidence inconclusive. For example, Macleod et al[43] argued that the association between cannabis use and psychological health problems is explicable in terms of influence from third factors such as childhood adversity, peer group, and family. Hereditary predisposition for psychosis is no doubt one important predictor of schizophrenia. Despite this, only one of the existing studies of the causal role of cannabis in the development of schizophrenia adjusts for the confounding effect of predisposition to psychosis in first-degree relatives,[37] and another study controls for family history of psychiatric illness.[41]

Causal effects of cannabis cannot be established from this study, and it would not be possible to establish cau-

sality from any observational study. However, the results clearly show that cannabis-induced psychoses do not occur randomly. Rather, the degree of hereditary predisposition in individuals who receive treatment of cannabis-induced psychosis closely mirrors that in those who develop schizophrenia with no history of cannabis-induced psychosis. The results agree with those of other studies that show that cannabis predominantly causes psychotic symptoms in those persons who are predisposed to develop psychosis or show signs of psychosis in the absence of cannabis use.[7,37,39,44,45]

STUDY LIMITATIONS

Some limitations of the present study merit discussion. The results were based on data from registers. As a result, none of the diagnoses assigned to the patients or their relatives could be confirmed. We have previously described how the diagnoses of cannabis-induced psychosis and schizophrenia can be partially validated.[9] Approximately one-third of the sample received outpatient treatment of a cannabis-induced psychosis, and admissions were generally short, which is consistent with a short-lived psychotic condition.[9] The diagnosis of schizophrenia assigned to the patients during follow-up was validated in that 73.9% of the patients received this diagnosis on at least 3 separate occasions.[9] The data set also did not include information about cannabis exposure. Therefore, it is not known whether the included individuals were regular or experimental cannabis users and what the level of cannabis exposure was immediately before the diagnosis of cannabis-induced psychosis was made. In addition, the registers do not contain information about predisposition to cannabis use, abuse, or dependence.

Information about psychiatric history in family members is gathered as part of the routine evaluation in patients receiving psychiatric treatment. This could lead to differences in the way patients with and without hereditary predisposition are treated. Psychiatrists are possibly more likely to diagnose schizophrenia rather than cannabis-induced psychosis in patients who exhibit psychoses after cannabis use if there is a positive family history of psychiatric disorders. However, the Figure was created to determine whether predisposition to psychiatric disorder has an effect on the absolute risk of schizophrenia or the timing of onset after a cannabis-induced psychosis. That the Figure shows similar trajectories for the cumulative incidences regardless of predisposition in family members indicates that such bias seems to be of minor importance.

Individuals were included in the study after having received psychiatric treatment. Consequently, they represent the more severe cases of cannabis-induced psychotic symptoms. The results may, therefore, not be generalizable to individuals who develop psychotic symptoms after cannabis use without requiring treatment or who develop psychotic symptoms that last less than 48 hours, which is required according to the *ICD-10*. This is important because a number of studies have shown that cannabis frequently induces short-lived psychotic symptoms both in nonpsychiatric samples and in individuals with schizophrenia.[46-50]

There is no adjustment for multiple testing of the comparisons given in the Table. Such adjustment would only strengthen the conclusion that rate ratios of predisposition to psychiatric disorders are similar in individuals treated because of a cannabis-induced psychosis and those with schizophrenia.

The incidence ratio of cannabis-induced psychosis in Denmark has been estimated to be 2.7 per 100 000 person-years.[9] To our knowledge, no publications describe the incidence of cannabis-induced psychosis in other countries. It is likely that diagnostic practices differ between countries. In addition, hashish use is common in Denmark, whereas marijuana is used more frequently in other parts of the world.[51] The delta-9-tetrahydrocannabinol content in hashish is much higher, and this compound is responsible for most of the psychoactive effects.[52] Both country-specific diagnostic practices and patterns of cannabis use could affect the generalizability of the results.

CONCLUSIONS

Psychotic symptoms after cannabis use should be taken extremely seriously. It is recommended that individuals with a cannabis-induced psychosis according to *ICD-10* criteria be treated as though the condition is a first sign of schizophrenia, regardless of predisposition to a psychiatric disorder. Psychotic symptoms after cannabis use that are short-lived or do not require treatment should be the focus of future prospective studies because such symptoms could be important indicators of risk of schizophrenia and other severe psychiatric disorders. In addition, future studies should compare the clinical course after cannabis-induced psychoses with that of other psychotic disorders.

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