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Association between age at onset of psychosis and age at onset of cannabis use in non-affective psychosis

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Abstract

Introduction—Several studies have associated cannabis use with the development of schizophrenia. However, it has been difficult to disentangle the effects of cannabis from that of other illicit drugs, as previous studies have not evaluated pure cannabis users. To test whether the onset of cannabis use had an effect on the initiation of psychosis, we examined the time relationship between onset of use and onset of psychosis, restricting our analysis to a cohort of individuals who only used cannabis and no other street drugs.

Methods—Fifty seven subjects with non-affective psychoses who used cannabis prior to developing a psychosis were interviewed using the Diagnostic Interview for Genetic Studies (DIGS). The Family Interview for Genetic Studies (FIGS) was also used to interview a family informant about psychiatric illness in the patient and the entire family. Multiple linear regression techniques were used to estimate the association between variables.

Results—After adjusting for potential confounding factors such as sex, age, lifetime diagnosis of alcohol abuse or dependence, and family history of schizophrenia, the age at onset of cannabis was significantly associated with age at onset of psychosis (β=0.4, 95% CI=0.1–0.7, p=0.004) and age at first hospitalization (β=0.4, 95% CI=0.1–0.8, p=0.008). The mean time between beginning to use cannabis and onset of psychosis was 7.0±4.3. Age at onset of alcohol use was not associated with age at onset of psychosis or age at first hospitalization.

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Conflict of interest

None of the authors have a conflict of interest relevant to this paper.

Contributors

JAGB participated in data collection, literature review and data analysis. JAGB wrote the first draft of this paper and the consecutive drafts were reviewed by AP, VT, MT, CC, JC, TM, and LD. AP, VT, MT participated in data collection. AP participated in literature review. LED directed the entire project.

Conclusion—Age at onset of cannabis is directly associated with age at onset of psychosis and age at first hospitalization. These associations remain significant after adjusting for potential confounding factors and are consistent with the hypothesis that cannabis could cause or precipitate the onset of psychosis after a prolonged period of time.

Keywords

cannabis; psychosis; age; sex; schizophrenia

1. Introduction

A number of clinical studies have found that cannabis use is associated with an earlier age at onset of psychosis in polysubstance abusers (Compton et al., 2009; Dragt et al., 2010), but little attention has been paid to whether the onset of cannabis use is actually associated with the onset of a psychosis. This should be examined by studying subjects whose cannabis use preceded the initiation of psychosis, and who have no history of any other drug use that could also lead to a psychosis. Unfortunately, most previous studies did not focus on people who solely abused cannabis (Barnes et al., 2006; Leeson et al., 2011). Thus, the objective of the current study was to focus solely on heavy cannabis users and study the association of age at onset of both cannabis use and psychosis as one measure of whether cannabis use is causally related to psychosis. If cannabis causes or precipitates the onset of psychosis, a significant association should be found between both ages of onset after adjusting for potential confounding factors.

2. Methods

2.1. Subjects

Eligible subjects were between the ages of 18 and 40, had a current diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or psychosis not otherwise specified, and had a history of heavy cannabis use before the onset of psychosis. They came from the New York City area and Boston, locations where the senior author LED resided. Subjects were not eliminated if they had a lifetime diagnosis of alcohol abuse or dependence, but they had to be in sustained full remission at the time of intake into the study. Heavy cannabis use was defined as a history of using cannabis 50 or more times in one year. Frequency of use during the heaviest period of cannabis use before the onset psychosis was defined on a 5 point Likert scale (0=one a month or less, 1=2–3 times a month, 3=weekly, 4=2–5 times a week, 5=daily). Age at onset of psychosis was defined as the age when the patient first experienced delusions, hallucinations, disorganized speech, disorganized or catatonic behavior. Age at onset of psychosis, age at first hospitalization and age at onset of cannabis use were recorded in years. Exclusion criteria included: lifetime recreational drug use other than cannabis more than 5 times, past or current medical history of clinically significant central nervous system disorders, any significant medical condition that could compromise ability to participate, and inability to give informed consent. Subjects were also excluded if cannabis use began after the onset of psychotic symptoms.

Fifty seven subjects participated in this study. Subjects were interviewed once their attending psychiatrist considered them stable and capable of providing written informed consent. Subjects were asked to provide a family informant to provide supplementary information if possible. All subjects signed a written informed consent and relatives who were interviewed gave written consent if seen in person or verbal consent if interviewed by phone. This study was approved by the Institutional Review Board of all participating institutions (Roosevelt-St. Luke's and Bellevue Hospitals, New York, NY; New York

University Medical Center; Corrigan Mental Health Center, Fall River, MA; VA Boston Healthcare System, Brockton, MA; Beth Israel Deaconess, McLean Hospitals Boston, MA).

2.2. Measures

Subjects were interviewed using the Diagnostic Interview for Genetic Studies (DIGS, version IV; Nurnberger et al., 1994). This instrument assessed the onset, pattern, course, comorbidity and chronology of psychotic, mood and substance abuse symptoms. Age at onset of psychosis and age at first hospitalization were obtained as part of this standardized instrument. Diagnoses were made using all available information including interviews with the patient, direct observation, information obtained from treating psychiatrists and family members, and medical records.

A family pedigree was drawn with information obtained from the participant and family informants. Family informants were interviewed regarding illnesses known to occur within the family using the Family Interview for Genetic Studies (NIH, 1992).

2.3. Data Analysis

Categorical and interval variables were compared using chi-square and the independent t-test statistics, respectively. Multiple linear regression analysis was used to estimate associations between variables. The main analysis estimated the association between age at onset of cannabis use and age at onset of alcohol with: 1) the age at onset of psychosis, and 2) the age at first hospitalization for a psychotic episode. The same associations were estimated after adjusting for potential confounding factors such as sex, age, lifetime diagnosis of alcohol abuse or dependence, and family history of schizophrenia in a first degree relative. All statistical analyses were performed using STATA 11.0.

3. Results

3.1. Demographic and clinical variables

The majority of the subjects in the sample were males (Table 1). Ages ranged from 18 to 39 years. A lifetime diagnosis of alcohol abuse or dependence was present in 24.6% of the sample. 64.9% of the subjects had a lifetime diagnosis of cannabis abuse or dependence. There were no differences between males and females in the age at onset of alcohol (15.5±2.9 vs. 15.5±3.5, p=0.491) or in the age at onset of cannabis (15.5±2.9 vs. 15.0±3.3, p=0.321). Furthermore, there were no differences between males and females in the age at onset of psychosis (22.1±4.0 vs. 23.7±5.1, p=0.865) or in the age at first hospitalization (22.5±4.2 vs. 23.9±5.3, p=0.816).

Schizophrenia and schizoaffective disorder were the most common diagnoses. The mean number of years between onset of cannabis and onset of psychosis was 7.0±4.3 (Table 1). All subjects used cannabis at least weekly and the majority of them used cannabis daily during the heaviest period of use. Age at onset of psychosis (β= −1.22, 95% CI= −2.8-0.4, p=0.129) and age at first hospitalization (β= −1.0, 95% CI= −2.8-0.7, p=0.253) were not associated with the amount of cannabis use as defined by the Likert scale described above. The length of the period between the onset of cannabis and the onset of psychosis was not associated with the amount of cannabis use (β= −0.1, 95% CI= −1.8-1.5, p=0.861). Age at onset of alcohol use was associated with age at onset of cannabis use (β=0.4, 95% CI= 0.1–0.7, p=0.020).

3.2. Association between age at onset of cannabis and alcohol, and age at onset of psychosis

There was a significant association between age at onset of cannabis use and age at onset of psychosis (β=0.4, 95% CI=0.1–0.8, p=0.015). This association remained significant after adjusting for potential confounding factors (Table 2). Age was also significant in the multivariate model, but sex and family history of schizophrenia were not. Even after excluding subjects with a lifetime diagnosis of alcohol abuse or dependence from the multivariate analysis, age at onset of cannabis use was still associated with age at onset of psychosis (β=0.4, 95% CI=0.1–0.7, p=0.009). Similar analyses were conducted for age at onset of alcohol, but there were no associations with age at onset of psychosis in the unadjusted model (β= −0.07, 95% CI= −0.5-0.3, p=0.733) or the adjusted model (β=−0.02, 95% CI= −0.3-0.3, p=0.907).

3.3. Association between age at onset of cannabis and alcohol, and age at first hospitalization

There was a trend for age at onset of cannabis use to be associated with age at first hospitalization in the unadjusted model (β=0.4, 95% CI= −0.1−0.8, p=0.080). The association became significant after adjusting for sex, age, lifetime diagnosis of alcohol abuse or dependence, and family history of schizophrenia (Table 3). Age at onset of cannabis use was associated with age at first hospitalization (β=0.5, 95% CI=0.1–0.9, p=0.015) even after subjects with a lifetime diagnosis of alcohol abuse or alcohol dependence were excluded from the analysis. A multiple linear regression was done to estimate the association between age at onset of alcohol and age at first hospitalization, but they were not associated in the unadjusted model (β=0.04, 95% CI= −0.4−0.5, p=0.834), or after adjusting for other covariates (β=0.1, 95% CI= − 0.2−0.5, p=0.474).

4. Discussion

The present study found that age at onset of cannabis use is directly associated with age at onset of psychosis or at first hospitalization among cannabis using subjects with non-affective psychosis who did not use other street drugs. These findings are consistent with the hypothesis that cannabis may have an effect on initiating the onset of psychosis, or even that psychosis may be a direct consequence of heavy cannabis use in some people. However, it should be noted that the amount of cannabis use was not associated with the time difference between beginning to use cannabis and onset of psychosis.

Only two previous studies specifically examined the association between age at onset of cannabis and age at onset of psychosis, but both included cohorts consisting of polysubstance users.Barnett et al. (2007) reported a significant correlation between age at onset of cannabis and psychosis, but they did not adjust for any potential confounders. Leeson et al (2011) found a significant association between age at onset of cannabis and age at onset of psychosis after adjusting for sex. In addition, cannabis use was associated with age at onset of the prodrome (Leeson et al, 2011; Compton et al., 2009). Most previous studies also do not distinguish whether cannabis users began using cannabis prior to the onset of psychosis or subsequent to it (Barnes et al., 2006; Barnett et al., 2007; Van Mastrigt et al., 2004). The current study only included subjects who started using cannabis before the onset of psychosis.

There are sex differences in the age at onset of psychosis and the prevalence of cannabis use (SAMHSA, 2011). In addition, it is alleged that subjects with younger onset of psychosis are more likely to use cannabis than those with older onset due to a cohort effect (Sugranyes et al., 2009). These facts suggest that the association between cannabis and psychosis could be

confounded by sex and age differences. The current study did not find sex differences in the age at onset of psychosis, first hospitalization or age at onset of cannabis use in any of our models. These findings are consistent with previous studies that supported the hypothesis that sex does not have any effect on the age at onset of psychosis after including the effect of cannabis use (Veen et al., 2004). Also, after adjusting their models by age, a recent meta-analysis consisting of polysubstance users and non substance users showed that drug use was associated with earlier onset of psychosis, and cannabis showed the strongest association (Large et al., 2011).

There is little evidence to support an effect of alcohol on hastening onset of a schizophrenia-like psychosis (Compton et al., 2009). In support of this, we found no association between age at onset of alcohol use, and age at onset of psychosis or age at first hospitalization. These results could reflect specificity of cannabis's effect on the onset of psychosis. Most important associations between cannabis and main outcome variables remained significant after excluding those subjects with history of alcohol abuse or dependence.

This current study had a number of limitations that should be noted. First, the cross sectional and retrospective self-report design of this study could contribute to biased reporting. Second, the ages at onset were recorded in years and thus not as precise as a more exact measure, such as months. Hence, it could have diminished the difference between age at onset of psychosis and age at first hospitalization. Nevertheless, diagnoses were made using a standardized instrument and all available information including interviews with the patient, direct observation, information obtained from treating psychiatrists and family members, and medical records. Third, it has been proposed that cannabis's effects on age at onset of psychosis would be mediated by a genetic vulnerability (Estrada et al., 2011). However, our small sample size may have limited the ability to find an association between family history of schizophrenia and the age at onset of psychosis. Fourth, this study did not measure the trajectory of cannabis use from first use until the onset of psychosis. However, we measured the frequency of cannabis use during the period of heaviest use before the onset of psychosis, and it was not associated with age at onset of psychosis or first hospitalization. Despite these negative results, limited inferences can be made due to recall bias and the nearly homogenous high level of cannabis use of this population. Nevertheless, some studies have found a stronger association between cannabis use and age at onset among heavy cannabis users than in sporadic users (Zammit et al., 2002). Conversely, a meta-analysis found no significant differences in age at onset of psychosis between heavy cannabis smokers and lighter ones (Large et al., 2011). Finally, this sample was composed of subjects with non-affective psychosis who only use cannabis and no other street drugs which limit the possibility of generalizing our results to other diagnostic groups.

In summary, this study found that age at onset of cannabis was directly associated with age at onset of psychosis and age at first hospitalization. Cannabis is not sufficient or necessary to trigger schizophrenia, but if cannabis use precipitates the onset of psychosis, efforts should be focused on designing interventions to discourage cannabis use in vulnerable individuals.

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Table 1

Sociodemographic and clinical characteristics of non-affective psychotic subjects.

	N=57 (%)
Males	47 (82.5)
Age (mean±SD)	25.2±5.0
Single	49 (87.5)
Student	7 (12.3)
Employed	11 (19.3)
Unemployed	39 (68.4)
Years of education (mean±SD)	12.5 (2.1)
African American	19(33.3)
White	15 (26.3)
Hispanic	12 (21.1)
Asian	3 (5.3)
More than one race	8 (14.0)
Age at onset of alcohol (mean±SD)	15.5 (3.0)
Alcohol abuse	9 (15.8)
Alcohol dependence	5 (8.8)
Age at onset of cannabis (mean±SD)	15.4 (3.0)
Cannabis abuse	19 (33.3)
Cannabis dependence	18 (31.6)
Weekly	6 (11.3)
2–5 times a week	16 (30.2)
Daily	31 (58.5)
Schizophreniform	2 (3.5)
Psychosis NOS	13 (22.8)
Schizoaffective	18 (31.6)
Schizophrenia	24 (42.1)
Age at onset of psychosis (mean±SD)	22.4 (4.2)
Age at first hospitalization (mean±SD)	22.8 (4.4)
First degree relative with schizophrenia	7 (12.7)

SD: standard deviation

Table 2

Adjusted association between age at onset of psychosis, age at onset of cannabis and other potential predictors among cannabis using subjects.

	β	95% confidence interval	p-value
Age at cannabis onset	0.4	0.1-0.7	0.004
Alcohol abuse/dependence	−0.1	−2.0-2.0	0.987
Age	0.6	0.4-0.7	<0.001
Sex	−0.8	−3.0-1.4	0.462
First degree relative with schizophrenia	−1.5	−4.2-1.2	0.268
Constant	2.6	−3.9-9.1	0.420

Age at cannabis onset: continuous variable

Age: continuous variable

Sex: 0-female, 1-male

First degree relative with schizophrenia: 0-no, 1-yes

Constant: regression model constant variable

Table 3

Adjusted association between age at first hospitalization for a psychotic episode, age at onset of cannabis and other potential predictors among cannabis using subjects.

	β	95% confidence interval	p-value
Age at cannabis onset	0.4	0.1-0.8	0.008
Alcohol abuse/dependence	0.9	−1.4-3.2	0.425
Age	0.6	0.4-0.8	<0.001
Sex	−0.3	−2.7-2.1	0.785
First degree relative with schizophrenia	−1.4	−4.5-1.7	0.364
Constant	1.2	−6.7-9.0	0.765

Age at cannabis onset: continuous variable

Age: continuous variable

Sex: 0-female, 1-male

First degree relative with schizophrenia: 0-no, 1-yes

Constant: regression model constant variable