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A controlled family study of cannabis users with and without psychosis

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ABSTRACT

Background: Cannabis is one of the most highly abused illicit drugs in the world. Several studies suggest a link between adolescent cannabis use and schizophrenia. An understanding of this link would have significant implications for legalization of cannabis and its medicinal value. The present study aims to determine whether familial morbid risk for schizophrenia is the crucial factor that underlies the association of adolescent cannabis use with the development of schizophrenia.

Methods: Consecutively obtained probands were recruited into four samples: sample 1: 87 non-psychotic controls with no drug use; sample 2: 84 non-psychotic controls with cannabis use; sample 3: 32 patients with a schizophrenia spectrum psychosis with no drug use; sample 4: 76 patients with schizophrenia spectrum psychosis with cannabis use. All cannabis using subjects used this drug during adolescence, and no other substance, with the exception of alcohol. Structured interviews of probands and family informants were used to obtain diagnostic information about probands and all their known relatives.

Results: There was an increased morbid risk for schizophrenia in relatives of the cannabis using and non-using patient samples compared with their respective non-psychotic control samples ($p = .002$, $p < .001$ respectively). There was no significant difference in morbid risk for schizophrenia between relatives of the patients who use or do not use cannabis ($p = .43$).

Conclusions: The results of the current study suggest that having an increased familial morbid risk for schizophrenia may be the underlying basis for schizophrenia in cannabis users and not cannabis use by itself.

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1. Background

Many studies have shown an association between cannabis use and schizophrenia (Compton et al., 2009; Galvez-Buccollini et al., 2012; Zammit et al., 2002). Compton et al.'s (2009) study and Galvez-Buccollini et al.'s (2012) study both found that cannabis use during adolescence may cause an earlier age of onset of psychosis than would have occurred in the absence of cannabis use. Galvez-Buccollini found a direct association between age of onset of cannabis use and age of onset of psychosis (Galvez-Buccollini et al., 2012). While neither study's findings could definitively point to cannabis as a causative factor in developing psychosis, both clearly identified it as a catalyst. An earlier study found an association between self-reported cannabis use and future hospital admission for schizophrenia related illness and also found a dose dependent relationship between frequency of cannabis use and risk for schizophrenia, with those who used cannabis more than 50 times at any point at the greatest risk of developing the illness (Zammit et al., 2002). Despite these findings, there has yet to be conclusive evidence that cannabis use may cause psychosis.

One leading theory is that a genetic predisposition may be necessary in persons who develop psychosis after using cannabis; however only several studies have been reported to date (Andréasson et al., 1989; Boydell et al., 2007; McGuire et al., 1995).

McGuire et al. (1995) examined schizophrenia patients who used cannabis, but did not include a non-psychotic control sample. This study found a significantly higher morbid risk of schizophrenia in the relatives of the patients who used cannabis and developed psychosis compared with schizophrenia patients who were non-cannabis users ($p = 0.02$). This result is contrary to what would be expected if cannabis could cause schizophrenia without the presence of an underlying genetic predisposition. In addition, without a non-psychotic control group, they could not address whether the rates of schizophrenia in relatives were greater than those in the general population. Moreover, as the patients studied were users of other substances in addition to cannabis, the effect of other substance abuse could not be separated from cannabis use.

Similarly, Boydell et al. (2007) studied first onset schizophrenia cases who either had or had not used cannabis prior to onset, and also had no control non-psychotic population. In this study, no difference was found for family history of schizophrenia between patient groups, again suggesting that cannabis alone does not lead to psychosis.

In contrast to these studies, one longitudinal study found that the relative risk for developing schizophrenia was increased in users of

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cannabis compared to non-users by 4.1 times, while there was no difference seen between the groups for family history of schizophrenia (Andréasson et al., 1989). This would suggest that it is the cannabis and not genetic predisposition that determines who develops schizophrenia after using cannabis. This study's results are questionable; however, as similar to the above studies, it did not control for other drug use. The n is also low, with only 8 cases and 13 controls. They also used only male participants, making it difficult to generalize to all patients with schizophrenia. These studies are the only ones to our knowledge that address the question of whether cannabis use can cause schizophrenia without an increased familial risk for the illness.

Other studies have examined alleles for specific candidate genes in an effort to determine whether they interact with cannabis to lead to a higher risk for psychosis. The first of such studies identified the COMT Val158Met polymorphism, as a candidate risk allele for schizophrenia when combined with premorbid cannabis use (Caspi et al., 2005). This has been called into question however; as later studies found that there was no effect of COMT variation (Glatt et al., 2003; Tovilla-Zárate et al., 2012; Zammit et al., 2007). Suchanek et al. (2013) more recently studied whether the Val66Met polymorphism of the BDNF gene may also interact with cannabis to put people at high risk for schizophrenia. However, it only had an association with earlier age of onset and not development of illness per se. With only few candidate genes having been identified and studied, whether any specific genetic predisposition increases risk for schizophrenia when cannabis is used has yet to be determined.

The present study, to our knowledge, is the first family study that examines both non-psychotic cannabis users and non-cannabis user controls as two additional independent samples, enabling the examination of whether the risk for schizophrenia is increased in family members of cannabis users who develop schizophrenia compared with cannabis users who do not and also whether that morbid risk is similar or different from that in family members of schizophrenia patients who never used cannabis. We hypothesize that a higher familial risk for schizophrenia will be found in people who have used cannabis during adolescence and later developed psychosis when compared to adolescent cannabis users who did not develop psychosis and will be no different from risk in families of people with schizophrenia in general; thus indicating that cannabis use alone is not likely to cause psychosis. Here we solely examined familial risk. For the purposes of this study, we have not explored any other possible risk factors that could be contributing to modified brain development during adolescence and acknowledge that others may be significant as well.

2. Methods

2.1. Subjects

Subjects came from the New York City metropolitan area where the PI (LED) was a professor in the Department of Psychiatry, New York University, Langone School of Medicine until 2011. On her relocation to Boston and the Department of Psychiatry at Harvard Medical School, the acquisition of subjects was expanded to the Boston area. Eligible subjects in both locations were between the ages of 16 and 40 and consisted of four samples:

Sample 1 Controls with no lifetime history of psychotic illness, cannabis, or any other drug use. 103 subjects were recruited and enrolled. After structured evaluations were complete, 12 subjects were excluded for exceeding the cannabis use criteria, one for use of ecstasy > 5 times in lifetime, two subjects did not have biologic relatives, and one subject was found to be related to another subject (final n = 87).

Sample 2 Controls with no lifetime history of psychotic illness, and a history of heavy cannabis use during adolescence, but no other drug use. 105 subjects were recruited and enrolled. After being interviewed and upon final diagnoses, 7 subjects were excluded for not meeting heavy cannabis use criteria, 6 were excluded for having used other drugs > 5 times in lifetime, 1 subject was excluded due to a parent's report that subject had a history of psychosis and treatment with antipsychotic, and 7 were excluded due to missing information on relatives (final n = 84).

Sample 3 Patients with no lifetime history of cannabis use or any other drug and less than 10 years of being ill. 38 subjects were recruited and enrolled. After being interviewed and upon final diagnoses, 2 subjects were excluded for exceeding cannabis use criteria and four were excluded due to missing information on relatives (final n = 32).

Sample 4 Patients with a history of heavy cannabis use and no other drug use during adolescence and prior to the onset of psychosis. 105 subjects were recruited and enrolled. After being interviewed and upon final diagnoses, 1 subject was excluded for not meeting diagnosis criteria for Axis 1 psychotic disorder, 2 were excluded for not meeting heavy cannabis use criteria, 2 were excluded for having used other drugs > 5 times in lifetime, and 11 were excluded due to missing information on relatives (final n = 76).

See Table 1 for a description of each sample.

Subjects with no drug use could not have used substances other than alcohol or tobacco more than 5 times during their lifetime. Heavy cannabis use was defined as a history of using cannabis 50 or more times in one year or a minimum of 5 times a week for at least 2 months during adolescence. Subjects were not eliminated if they had a lifetime diagnosis of alcohol abuse or dependence, but they had to be in sustained full remission from alcohol use at the time of intake into the study. Probands reporting past alcohol abuse per sample were as follows: sample 1: 5 (5.7%), sample 2: 13 (16.0%), sample 3: 5 (15.6%), and sample 4: 23 (29.1%). Other exclusion criteria included: 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. As this study examines cannabis use prior to onset of psychosis, subjects were also excluded if cannabis use began after the onset of psychotic symptoms.

The recruitment of non-psychotic controls (with and without cannabis use) was completed by advertisement in local newspapers, Craigslist.org and by flyer in universities. The advertisement was for men and women between the ages of 18 and 40 interested in participating in research on marijuana use who did or did not have a history of its use. The goal was for an approximate equal number of male and female controls in both non-psychotic samples. Patients were recruited by obtaining potential participants from consecutive admissions to acute psychiatric hospital wards during the years of this study (2007–2012). The hospital units included in this study were admission wards at Bellevue and St. Luke's and Roosevelt Hospitals in New York City; VA Boston Healthcare System, Brockton; Beth Israel Deaconess Hospital, Boston; McLean Hospital, Belmont; Corrigan Mental Health Center, Fall River all in Massachusetts. Recruitment lasted much longer than expected

Table 1
Number of subjects and relatives by sample.

	Sample 1 (n = 87)	Sample 2 (n = 84)	Sample 3 (n = 32)	Sample 4 (n = 79)
Probands	m = 42; f = 45	m = 40; f = 44	m = 15; f = 17	m = 60; f = 16
First degree relatives	338	333	137	360
Total relatives	1234	1517	460	1080

Chi^2 tests found no significant sex differences between groups.