



## 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 anti-psychotic, 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, [Craigslis.org](http://Craigslis.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 ( <i>n</i> = 87)	Sample 2 ( <i>n</i> = 84)	Sample 3 ( <i>n</i> = 32)	Sample 4 ( <i>n</i> = 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<sup>2</sup> tests found no significant sex differences between groups.

for this study particularly because of the difficulty finding patients who did not use other drugs in addition to cannabis and the difficulty finding patients who did not use any drugs at all during adolescence.

Interviews were completed once subject's treating psychiatrist considered him/her stable and capable of providing written informed consent. Subjects were asked to provide contact information for a family informant who could give detailed family history information. All available family informants were then contacted and interviewed. All subjects signed written informed consent and relatives gave written consent if seen in person or verbal consent if interviewed by phone. This study and its procedures were approved by the Institutional Review Boards of all the above hospitals where patients were recruited as well as The Nathan Kline Institute, New York University, The VA Boston Healthcare System, and Harvard Medical School, as these institutions approved and oversaw the overall project.

## 2.2. Measures

Study probands were interviewed using a modified version of the Diagnostic Interview for Genetic Studies version IV (DIGS; obtained from website: [https://www.nimhgenetics.org/interviews/digs\\_4.0\\_bp/](https://www.nimhgenetics.org/interviews/digs_4.0_bp/)), a structured diagnostic interview which was supplemented with detailed substance abuse questions (Nurnberger et al., 1994). Family informants were interviewed regarding illnesses known to occur within the family using the Family Interview for Genetic Studies (FIGS; obtained from website: [https://www.nimhgenetics.org/interviews/figs/FIGS\\_4.0.pdf](https://www.nimhgenetics.org/interviews/figs/FIGS_4.0.pdf)) (NIH, 1992). Information about all first-, second-, and third-degree relatives was obtained, as well as information about any other relative who had a known psychiatric illness. They were also asked questions regarding the proband to supplement diagnostic information. Best estimate diagnoses were made for all probands using information from all available sources including the DIGS, family informant interview, and medical records.

A family pedigree was drawn with information obtained from the proband, family informants, and information obtained from patient medical records when available. The pedigree included information on the age and sex of all known relatives. Questions were asked during the FIGS interview regarding any clinically significant psychiatric problems of all relatives, such as any history of any known hospitalizations, psychiatric medications, problems with drugs or alcohol, and suicides.

All interviews were conducted by trained research assistants with prior experience working with patients with schizophrenia. Diagnoses were made for all family members using information from the interviews with the proband and the family informant. Two research psychiatrists (LED and JG-B) completed all best-estimate diagnoses.

## 2.3. Data analysis

Morbid risk (MR) for relatives of probands was determined by examining all known relatives on whom information had been gathered using the Weinberg method for age correction. Weinberg's method accounts for individuals according to their age, and where they are in relation to the period of risk for an illness. The equation is as follows; where A is the number of affected individuals who make a whole contribution, U<sub>2</sub> is the number of unaffected individuals in the risk period and thus only making half a contribution, U<sub>3</sub> is the number of unaffected individuals who passed through the risk period and make a whole contribution (McGuire et al., 1995).

$$\text{Morbid Risk} = \frac{A}{A + U_2/2 + U_3}$$

Morbid risk (MR) was determined for schizophrenia and other disorders in all probands and between group analyses were conducted. MR is the age corrected illness frequency in the relatives of probands. It is a better measure than prevalence because it also includes an estimate of those who are at risk of developing mental illness in the future by taking age at the time of interview into account.

Using the age distribution for our sample and past research, the period of risk used for schizophrenia and related disorders, bipolar disorder, and drug abuse was 17–45 while depression was 15–59 (Fuchs et al., 2010; McGuire et al., 1995; Varma and Sharma, 1993).

In addition, another set of analyses was completed, whereby families were analyzed as a unit, and an affected family was counted as one despite the number of relatives with the illness within the family. The number of families positive for illness was recorded.

All analyses were performed independently for history of schizophrenia, bipolar disorder, depression, and drug abuse in relatives. We also looked at history of depression and mania in probands to see any association with morbid risk for affective disorders in relatives.

Between-group analyses were performed using chi-squares and Fisher's exact tests when 20% or more of the expected cell frequencies were below five.

## 3. Results

### 3.1. Schizophrenia in relatives

Familial aggregation of schizophrenia in first-degree relatives (FDRs) is presented in Table 2. FDR of cannabis using patients had a significantly higher MR for schizophrenia than the cannabis using controls ( $p = .002$ ). No significant differences in MR for schizophrenia in the FDR of patients who use or do not use cannabis were found

**Table 2**

Lifetime morbid risk of psychiatric illnesses for first degree relatives (FDR) of probands with schizophrenia and controls, with regard to cannabis use.

Diagnosis	FDR of sample 1 n = 338			FDR of sample 2 n = 333			FDR of sample 3 n = 137			FDR of sample 4 n = 360		
	A	BZ	MR%	A	BZ	MR%	A	BZ	MR%	A	BZ	MR%
Schizophrenia	3	265	1.4	2	200.5	1.0	8	88	9.1	14	215	6.5
Bipolar disorder	3	215.5	1.4	6	203.5	3.0	3	87	3.4	13	216	6.0
Depression	18	201	9.1	29	187.5	15.5	9	84.5	10.7	28	201	13.9
Drug abuse	12	219.5	5.5	47	213.5	22.0	10	90	11.1	23	219	10.5

A is number of affected relatives; BZ is age-corrected number of relatives; MR% is morbid risk.

Significant between sample comparisons:

Samples 1 vs 2: Drug abuse  $X^2 = 25.17$ ,  $p < .001$ .

Samples 1 vs 3: Schizophrenia,  $p < .001$ .

Samples 1 vs 4: Schizophrenia,  $p = .001$ ; Bipolar,  $p = .008$ .

Samples 2 vs 3: Schizophrenia,  $p = .001$ ; Drug abuse  $X^2 = 4.90$ ,  $p = .03$ .

Samples 2 vs 4: Schizophrenia,  $p = .002$ ; Drug abuse  $X^2 = 10.49$ ,  $p = .002$ .

**Table 3**  
Lifetime morbid risk of psychiatric illnesses for all relatives of probands with schizophrenia and controls, with regard to cannabis use.

Diagnosis	All relatives of sample 1 n = 1234			All relatives of sample 2 n = 1517			All relatives of sample 3 n = 460			All relatives of sample 4 n = 1080		
	A	BZ	MR%	A	BZ	MR%	A	BZ	MR%	A	BZ	MR%
Schizophrenia	7	794.5	0.9	12	874	1.4	13	315.5	4.1	38	718.5	5.3
Bipolar disorder	9	803	1.1	12	876.5	1.4	7	315.5	2.2	26	718	3.6
Depression	27	687.5	3.4	42	779.5	5.4	21	273.5	7.7	64	615	10.4
Drug abuse	36	811	4.4	87	897.5	9.7	21	317.5	6.6	50	724.5	6.9

A is number of affected relatives; BZ is age-corrected number of relatives; MR% is morbid risk.

Significant between sample comparisons:

Samples 1 vs 2: Drug Abuse  $X^2 = 17.58$ ,  $p < .001$ .

Samples 1 vs 3: Schizophrenia  $X^2 = 13.37$ ,  $p < .001$ ; Depression  $X^2 = 5.78$ ,  $p = .01$ .

Samples 1 vs 4: Schizophrenia  $X^2 = 25.40$ ,  $p < .001$ ; Bipolar  $X^2 = 13.04$ ,  $p < .001$ ; Depression  $X^2 = 21.00$ ,  $p < .001$ ; Drug Abuse  $X^2 = 4.37$ ,  $p = .04$ .

Samples 2 vs 3: Schizophrenia  $X^2 = 8.48$ ,  $p = .004$ .

Samples 2 vs 4: Schizophrenia  $X^2 = 19.86$ ,  $p < .001$ ; Bipolar  $X^2 = 8.62$ ,  $p = .003$ ; Depression  $X^2 = 12.35$ ,  $p < .001$ ; Drug Abuse  $X^2 = 4.05$ ,  $p = .04$ .

( $p = .43$ ). There was also no difference in MR for schizophrenia for FDR of controls who use or do not use cannabis ( $p = .34$ ) (Table 2). There were no significant changes in MR when all relatives were included (Table 3).

When families were analyzed as units, they were first compared by those who had a first degree family member affected by schizophrenia, and then by those families with any degree relative affected by schizophrenia. All results were similar to the above MR calculations (Tables 4 and 5).

### 3.2. Bipolar disorder in relatives

Familial aggregation of bipolar disorder in FDR is presented in Table 2. FDR of non-cannabis using controls had the lowest MR for bipolar disorder, while the FDR of cannabis using patients had the highest MR. There was no significant difference found between FDR of patients who used cannabis and the FDR of patients who did not use cannabis ( $p = .16$ ). Analysis of all relatives also found that relatives of patients with schizophrenia who use cannabis had a higher MR for bipolar disorder than relatives of controls who use cannabis ( $p = .003$ ) (Table 3).

When families were analyzed as units, there was no significant difference in prevalence of bipolar disorder in FDR of cannabis using patients compared to the FDR of cannabis using controls ( $p = 0.08$ ). There was also no difference in MR when FDR of non-cannabis using patients was compared to the FDR of non-cannabis using controls ( $p = 0.15$ ). Results were similar when all relatives were considered in the family analyses (Table 5).

In sample 4, we found an association between mania in the probands and bipolar disorder in their FDR ( $p = <.001$ ). There was no association

seen in sample 3. In samples 1 and 2, there were no probands diagnosed with mania.

### 3.3. Depression in relatives

No significant differences in MR were observed in FDR of the samples.

A significant difference was observed between the two non-cannabis using groups, with relatives of non-cannabis using patients being at elevated risk for depression when all relatives were considered ( $p = .01$ ). There was also a difference seen between all relatives of cannabis using patients compared to the relatives of the cannabis using controls, with the relatives of the patients having increased risk ( $p < .001$ ) (Table 3).

No significant differences were observed between groups when families were analyzed as units (Tables 4, 5).

### 3.4. Drug abuse in relatives

Familial aggregation of drug abuse in FDR is presented in Table 2. FDR of cannabis using controls had a fourfold increase in MR for drug abuse over the FDR of non-cannabis using controls. There was significantly higher MR for drug abuse in FDR of cannabis using controls than the FDR of cannabis using patients ( $p = .002$ ). Results were similar when all relatives were included in the analysis (Table 3).

When families were analyzed as units, there was an elevated risk of drug abuse in FDR and all relatives of the families of controls with cannabis use when compared with controls without cannabis use (Tables 4, 5). There was significantly higher risk for drug abuse in FDR

**Table 4**  
Families with first degree relatives affected by psychiatric illnesses.

Diagnosis	Families of sample 1 n = 87		Families of sample 2 n = 84		Families of sample 3 n = 32		Families of sample 4 n = 76	
	A	%	A	%	A	%	A	%
Schizophrenia	3	3.4	2	2.4	5	15.6	9	11.8
Bipolar disorder	3	3.4	6	7.1	3	9.4	12	15.8
Depression	17	19.5	23	27.4	7	21.9	22	29.0
Drug abuse	11	12.6	30	35.7	7	21.9	16	21.1

A is number of affected families; % is percentage of affected families.

Significant between sample comparisons:

Samples 1 vs 2: Drug Abuse  $X^2 = 12.75$ ,  $p < .001$ .

Samples 1 vs 3: Schizophrenia,  $p = .03$ .

Samples 1 vs 4: Schizophrenia,  $p < .001$ ; Bipolar  $p = .001$ .

Samples 2 vs 3: Schizophrenia,  $p = .02$ .

Samples 2 vs 4: Schizophrenia,  $p = .02$ ; Drug Abuse  $X^2 = 4.19$ ,  $p = .04$ .

**Table 5**  
Families with any degree relative affected by psychiatric illnesses.

Diagnosis	Families of sample 1 n = 87		Families of sample 2 n = 84		Families of sample 3 n = 32		Families of sample 4 n = 76	
	A	%	A	%	A	%	A	%
Schizophrenia	5	5.8	10	11.9	8	25.0	24	31.2
Bipolar disorder	8	9.2	11	13.1	6	18.8	20	26.0
Depression	24	27.6	31	36.9	12	37.5	29	37.7
Drug abuse	21	24.1	35	41.7	11	34.4	25	32.5

A is number of affected families; % is percentage of affected families.

Significant between sample comparisons:

Samples 1 vs 2: Drug Abuse  $X^2 = 6.20$ ,  $p = .02$ .

Samples 1 vs 3: Schizophrenia  $X^2 = 9.07$ ,  $p = .003$ .

Samples 1 vs 4: Schizophrenia  $X^2 = 18.79$ ,  $p < .001$ ; Bipolar  $X^2 = 8.55$ ,  $p = .004$ .

Samples 2 vs 4: Schizophrenia  $X^2 = 9.23$ ,  $p = .002$ .

of cannabis using controls than the FDR of cannabis using patients only when families with affected FDR were considered ( $p = .04$ ) (Table 4).

#### 4. Discussion

This study aimed to determine whether people who use cannabis during adolescence have a greater risk for developing schizophrenia because they have an increased familial risk for the illness, and thus have a genetic predisposition for developing it regardless of cannabis use. If this is the case, we would expect to find a significantly higher morbid risk for schizophrenia in the relatives of people who develop schizophrenia compared to the relatives of non-schizophrenia controls, regardless of whether they do or do not use cannabis. The results of the current study, both when analyzed using morbid risk and family frequency calculations, suggest that having an increased familial risk for schizophrenia is the underlying basis for schizophrenia in these samples and not the cannabis use. While cannabis may have an effect on the age of onset of schizophrenia it is unlikely to be the cause of illness (Compton et al., 2009; Galvez-Buccollini et al., 2012). The current study, however, is not able to address whether cannabis can interact with a genetic predisposition to cause schizophrenia. In order to test this hypothesis, future longitudinal studies examining individuals at high familial risk for schizophrenia who do and do not abuse cannabis are needed. If when essentially controlling for genetic risk, those who use cannabis are significantly more likely to develop a schizophrenia-like illness than those who do not, a gene–cannabis abuse interaction is likely.

One advantage of the current study over past attempts to determine the cannabis–gene relationship is that only individuals who used cannabis and no other drugs were recruited, allowing the specific relationship of cannabis to schizophrenia to be determined without the confounding effects of other drug use.

When the design for this study was developed, it was determined necessary to explore history of all psychiatric diagnoses in relatives, and thus questionnaires were structured to record symptoms observed, as well as diagnoses given by clinicians. It was reasoned that other diagnoses, as well as schizophrenia, in family members would be important to examine as controls for our hypothesis, as well as to explore whether any genetic tendency for other disorders was also present. Given that psychotic symptoms may often be present in people having a diagnosis of bipolar disorder or major depression and that some researchers have shown evidence that there may be a genetic overlap between them (e.g. Smoller, 2013), our family study was conducted to uncover relatives with diagnoses of all psychiatric disorders, not just schizophrenia. In general, we found a tendency for depression and bipolar disorder to be increased in the relatives of cannabis users in both the patient and control samples. This might suggest that cannabis users are more prone to affective disorders than their non-using samples or vice versa. Future research may clarify this observation.

Drug abuse is present more frequently in family members of all 3 samples compared to those of non-cannabis abusing controls. This is in line with past research confirming a genetic predisposition for drug use (Merikangas et al., 1998; Merikangas et al., 2009). There is also a higher MR of drug abuse in the relatives of non-cannabis using patients than the non-cannabis using controls. While it is not significant ( $p = .09$ ), it suggests a trend that has also been seen in at least one previous study for relatives of samples of patients with schizophrenia to have higher risk for drug use (Gershon et al., 1988). An interesting difference is also seen between the relatives of cannabis using controls and cannabis using patients, where the relatives of controls have significantly greater MR for drug abuse than those of the patient sample. This is even seen when families are analyzed as a unit by affected FDR (Table 4). This indicates that while controls have a severely elevated genetic predisposition to use cannabis, the patient sample with comparable use is lacking an equivalent predisposition, and yet uses just the same. This could suggest that these individuals are using cannabis as a

form of self-medication and not because they have a predisposition for drug abuse per se.

There were several limitations to this study that should be mentioned. The most important is that our sample size for each sample is small. Our exclusion criterion of eliminating people who used any other drug besides cannabis was quite stringent and resulted in the elimination of many subjects who might otherwise have qualified for this study. However, we thought it was important to maintain this rule, if we expected to specifically examine the effects of cannabis. If other substance use was allowed in the samples, results could always be partially explained by their use.

One other important limitation to our study is that cannabis/marijuana as purchased on the streets of Boston and New York City has great variation in the amount of THC (Tetrahydrocannabinol) and CBD (Cannabidiol) contained in each unit of purchase. The amount of THC is particularly of concern, whereas CBD is the component that is thought to have medicinal value even in schizophrenia (Deiana, 2013). Unfortunately what proportions were of use in both cities at that time is not known.

Our other study limitations include the possibility of misdiagnosis, error, or false negatives, in obtaining information from both probands and family members by recall. We did not conduct personal direct interviews with each family member, but rather relied on history given to us by other members. Nevertheless, the family history method has been a valid and reliable tool for obtaining information when in-person interviews of relatives are not feasible.

In summary, we conclude that cannabis does not cause psychosis by itself. In genetically vulnerable individuals, while cannabis may modify the illness onset, severity and outcome, there is no evidence from this study that it can cause the psychosis. Future longitudinal studies examining people at genetic high risk for schizophrenia to determine whether those who later convert to a psychotic illness more frequently used cannabis than those who did not convert would clarify whether cannabis may interact with a genetic vulnerability to cause schizophrenia.

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None.

#### Contributors

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#### Conflict of interest

No co-authors had any conflict of interest.

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