

Cannabis and other variables affecting age at onset in a schizophrenia founder population

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Abstract

Objective: An ongoing collaborative study between the Human Neurogenetic Laboratory of Rockefeller University, New York and the Department of Psychiatry at the University of Pretoria, has been taking place since 1997, to map genes for schizophrenia. Aspects of cannabis use/abuse will be reported. **Method:** The Diagnostic Interview for Genetic Studies [DIGS] is used for all diagnosis. A narrative report is completed. From this database we determined: gender, diagnostic subtype, age of illness onset, early insults, early deviant behaviour, cannabis use/abuse and family history of schizophrenia. **Results:** From 341 subjects we found: 61% [n=209] males and 39% [n=132] females. In males, 75% [n=156] had schizophrenia and 25% [n=53] schizoaffective disorder [SAD]. In females 74% [n=97] had schizophrenia and 26% [n=35] SAD. 35% of subjects, [n=118], 44% [n=91] males and 20% [n=27] female's used/abused cannabis. The mean age at onset of illness for the males was 20.5 years. This is significantly earlier than that of males with no cannabis use/abuse group as well as for both these groups in females. The long-term course of illness was similar in both cannabis use/abuse and non-use/abuse groups. An analysis of variance was used to determine the contribution of different factors in determining the age of criteria onset. According to the results obtained, early deviant behaviour was the most important determining age of criteria onset. The group with the lowest mean age of criteria were male users of cannabis with severe early deviant behaviour [18,4 years]. **Conclusion:** Cannabis use/abuse is common amongst male schizophrenia subjects, and affects age at onset of illness. Early deviant behaviour in the first ten years of life in these subjects is more important in this regard, and may be seen as a possible endophenotypic marker.

Keywords: Cannabis; Psychosis; Schizophrenia; Founder population

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Introduction

Community surveys reveal that cannabis is the illicit drug of choice in South Africa. Lifetime rates of 32% in males and 13,1% in females were reported for cannabis use in a representative sample of grade 11 students in Cape Town. Cannabis has the second most common lifetime prevalence rate after alcohol.¹ The predominance of cannabis abuse in South Africa is also reflected in statistics gathered from specialist substance treatment centres. Between July and December 2003, 20% to 40% of patients in various substance

treatment centres scattered across South Africa reported cannabis to be their primary drug of abuse. Their average age was 20 to 21 years.²

People who suffer from psychotic illnesses are far more likely to consume cannabis than the general population. The question arises as to whether this is because the psychotic subjects use cannabis to alleviate their symptoms or whether cannabis use is a risk factor in precipitating their condition.

The nature of this link is not yet fully understood. The findings drawn from clinical samples of subjects identified with schizophrenia have limited value in shedding light on the mechanism underlying this association. In these cases the potential confounding factors linked to the clinical status of the subjects are difficult to control.³

However, data from clinical samples of subjects suffering from schizophrenia may shed some light on how cannabis use/abuse may affect factors such as age at onset of illness and the

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longitudinal course of the illness. Furthermore, the interaction of cannabis use/abuse with factors such as gender, early deviant behaviour in the first ten years of life, family history of schizophrenia in first and second-degree relatives and early insults (prenatal, perinatal and postnatal) can be investigated.

We report on some of this information as collected in a genetic database of Afrikaners with schizophrenia.

Method

A collaborative study on the genetics of schizophrenia in an Afrikaner founder population has been conducted since 1997. Subjects are recruited by the Department of Psychiatry at the University of Pretoria, South Africa and genetic analyses are undertaken by the Human Neurogenetics Laboratory at Rockefeller University in New York. The findings of this research have thus far has been published elsewhere.^{4,5} The clinical database of this ongoing study contains information obtained from the Diagnostic Interview for Genetic Studies (DIGS), a chronological summary report of each subject and other sources of information.⁴

This database provided the following information for 341 subjects included in the study thus far:

- Subject identification number and initials
- Gender
- Age at the time of initial recruitment
- Age at which the subject meets the criteria for the onset of schizophrenia
- Previous hospitalization
- Longitudinal course of illness, including:
 - Episodic course of illness with interepisodic residual symptoms
 - Episodic course of illness with no interepisodic residual symptoms
 - Continuous course of illness
 - Single episode psychosis with partial remission
 - Single episode of psychosis with full remission
- Cannabis use:
 - Cannabis use [< 21 times a year]
 - Cannabis heavy use [> 21 times a year]
 - Use/abuse prior to onset of schizophrenia
- Schizophrenia diagnostic entities according to the DSM-IV, including:
 - Schizophrenia
 - Schizoaffective disorder (depressed type)
 - Schizoaffective disorder (bipolar type)
- Early deviant behaviour in the first 10 years of life (poor socialization, extreme fears/chronic sadness, and/or attention/learning impairment). – absent, poorly present, strongly present
- Family history of schizophrenia – absent, first-degree relatives, second-degree relatives
- Early insults (birth and perinatal)

The above data were coded and prepared on a spreadsheet. The statistical methods of analysis included basic descriptive statistics to summarize the data, chi-squared tests of independence between different factors and an analysis of the subject meeting the criteria for the onset of the disease/schizophrenia.

Ethical approval of this study was obtained from the Ethical

Review Board at the University of Pretoria, South Africa and the Rockefeller University, New York, USA.

Results

The mean age at the time of the DIGS interview was 34,09 years for all subjects. The mean criteria onset age was 23,5 years and the mean age of onset of symptoms was 21,5 years. There were 209 males (61%) and 132 females (39%) in the total study group. Of the total sample 60,12% ($n = 205$) of the total sample did not use/abuse cannabis, whereas 34,6% ($n = 118$) did use/abuse cannabis. In 5,28% ($n = 18$) of subjects this information was unknown. Twenty seven percent ($n = 91$) of the subjects reported use of cannabis prior to onset of illness. Eighty patients (24%) reported current use or heavy use as well as prior use. Seven patients (2%) have once used cannabis, but are not using it any more. The age of first use of cannabis was not reported in this study. Early deviant behaviour was reported by 60,71% ($n = 207$) of all patients, and was partly present (mild) in 29,33% ($n = 100$) of cases and strongly present (severe) in 31,38% ($n = 107$) of cases. The study group consisted primary patients ($n=260$) and family members ($n = 81$) who had also been diagnosed with schizophrenia. Of all the primary patients 25,38% ($n=66$) had a first-degree and 13,08% ($n=34$) a second-degree relative with schizophrenia.

The total sample comprised 74,19% ($n=253$), 11,14% ($n=38$) and 14,66% ($n=50$) of the three diagnostic groups, namely DSM-IV schizophrenia, SAD (depressed type) and SAD (bipolar type) respectively [SAD - Schizo Affective Disorder].

Early insults were reported by 35,2% ($n = 120$) of all patients, 51,9% ($n = 177$) reported that they did not have any early insults and in 12,9% ($n = 44$) of cases no information was available.

The number of previous hospitalizations ranged between 0 and 20. A percentage of 11,48 of patients did not have any previous hospitalizations while 70,7% ($n = 234$) of patients had been hospitalized three times or less.

A summary of the longitudinal course of the illness for the 281 patients for whom the information is known is given in Table I.

Table I: Longitudinal course of illness for 281 patients	
<i>Longitudinal course</i>	<i>Percentage</i>
Episodic course of illness with interepisodic residual symptoms	9,6% ($n = 27$)
Episodic course of illness with no interepisodic residual symptoms	21,4% ($n = 60$)
Continuous course of illness	42,4% ($n = 119$)
Single episode psychosis with partial remission	23,1% ($n = 65$)
Single episode of psychosis with full remission	3,6% ($n = 10$)

In the total sample of the males, 43,54% ($n = 91$) used/abused cannabis while the corresponding figure for females was only 20,45% ($n = 27$). In a small percentage of cases the information was not known. A statistically significant larger proportion of males than females used/abused cannabis ($p = < 0,0001$). This trend was also discernible in the group with heavy cannabis use. A statistically significant larger proportion of males (30,14%, $n = 63$) than females (8,33%, $n = 16$) reported heavy use (more than 21 times per year) ($p < 0,0001$).

Although the study group revealed no significant relation between cannabis use/abuse and the number of previous hospitalizations, it was found that of those subjects who did not

use/abuse cannabis 14,07% (n = 28) had never been hospitalized while the corresponding figure for the cannabis use/abuse group was 8,77% (n = 10).

Table II gives a comparison of the longitudinal course of illness for the cannabis use/abuse and non-use/abuse group. The percentages are similar for the two groups, although a slightly higher percentage of cannabis users (45%) were classified as having had a continuous course of illness than non-users (38%) and there was a slightly lower percentage of cannabis users with a single episode of psychosis with full remission (1%) versus non-users (5,4%). These differences were not significant.

Longitudinal course	Cannabis group	
	Non-use/abuse group	Use/abuse group
Episodic course of illness with interepisodic residual symptoms	10,24% (n = 17)	9% (n = 9)
Episodic course of illness with no interepisodic residual symptoms	21,69% (n = 36)	22% (n = 22)
Continuous course of illness	37,95% (n = 63)	45% (n = 45)
Single episode psychosis with partial remission	24,7% (n = 41)	23% (n = 23)
Single episode of psychosis with full remission	5,42% (n = 9)	1% (n = 1)

An analysis of variance was used to determine the contribution of different factors in determining the age of criteria onset. Factors considered were cannabis use, gender, family history of schizophrenia, early deviant behaviour, the occurrence of early insults and interactions between cannabis use on the one hand and gender, family history, early deviant behaviour and early insults on the other. A gender early deviant behaviour interaction was also included in the model. We included various factors in the model in view of the complex correlation structure of the different factors. A total of 256 patients' data was used for the analysis of variance. Only one representative per family (the primary patient) was used and subjects with incomplete data were excluded. Least squares means are reported throughout, since they are the best estimates of the true marginal population means when the design is unbalanced (unequal number of respondents per subgroup) and when there are interactive terms in the model.

The estimated mean age of cannabis users (22,7 years) was lower than that of non-users (24,4 years; $p = 0,1191$). The age of criteria onset was significantly different for males and females in this study. The mean age of criteria onset for males was estimated to be 21,62 years while that for females was 24,7 years ($p = 0,0208$). The interactive effect of gender and cannabis use was also significant in explaining the age of criteria onset ($p = 0,0197$). In Table III it can be seen that the effect of cannabis use on age of criteria onset was not the same for the two genders. The mean age of criteria onset of

Gender	Cannabis group	
	Non-use/abuse group	Use/abuse group
Male	24,6 years	20,4 years
Female	24,3 years	25,0 years

males who did not use cannabis (24,6 years) was significantly older ($p=0,0124$) than that of males who did (20,4 years), while the mean ages of females who used and did not use cannabis were similar (25,0 years and 24,3 years respectively). The mean age of criteria onset of male users was significantly younger than that of both female users ($p = 0,025$) and female non-users ($p = 0,0317$).

According to the results obtained, early deviant behaviour was the most important factor determining age of criteria onset ($p = 0,0037$). The mean age of the group with no early deviant behaviour (25,7 years) was significantly older than that of both those with less severe (22,9 years; $p = 0,0219$) and more severe (22,1 years; $p = 0,0024$) early deviant behaviour.

Although the interactive effect of substance use and early deviant behaviour was not significant in the model, there was a difference in the effect of early deviant behaviour between cannabis users and non-users. In the group using cannabis there was no significant difference in age of criteria onset between those without and with early deviant behaviour, while in the non-user group the age of criteria onset of those with no early deviant behaviour (27 years) was significantly older than that of those with severe early deviant behaviour (22,8 years; $p = 0,0169$). It can be seen in Table IV that the mean age of criteria onset decreases with the severity of the deviant behaviour in both groups, as expected, and that the non-users' mean age of criteria onset was consistently older than that of the cannabis users in all three behavioural groups.

Early deviant behaviour	Cannabis group	
	Non-use/abuse group	Use/abuse group
None	27,0 years	24,5 years
Mild	23,5 years	22,3 years
Severe	22,8 years	21,3 years

Gender and early deviant behaviour interaction was a significant, albeit marginally so, source of variation of criteria onset age ($p = 0,0543$). This implies that the effect of early deviant behaviour is not the same for males and females. The mean age of criteria onset of males with no (23,8 years; $p = 0,0339$) and males with less severe early deviant behaviour (23,5 years; $p = 0,0572$) was significantly higher than that of males with severe early deviant behaviour (20,1 years; p -values given). The mean age of females with no early deviant behaviour (27,6 years) was significantly higher than that of females with less severe (22,3 years; $p = 0,0299$) early deviant behaviour, while the difference was not significant between females with no and females with severe (24,1 years; $p = 0,1905$) early deviant behaviour (Table V).

Males with severe early deviant behaviour comprise the group with the youngest estimated mean age of criteria onset (Table V). The difference is significant at least at the 10% level

Early deviant behaviour	Gender	
	Male	Female
No	23,8 years	27,6 years
Mild	23,5 years	22,3 years
Severe	20,1 years	24,1 years

in all cases except from females with mild early deviant behaviour.

The mean age of males with severe early deviant behaviour (edb) was significantly younger than that of males with no edb ($p=0,0339$), males with mild edb ($p=0,0572$), females with no edb ($p<0,0001$) and females with severe edb ($p=0,0934$).

Table VI gives the mean age of criteria onset for the three characteristics: gender, cannabis use and early deviant behaviour. There is no statistically significant interaction between the three characteristics, but the results are interesting and consistent with the expectations of the researchers.

Table VI: Mean age of criteria onset of cannabis, early deviant behaviour and gender groups				
	Gender			
	Male		Female	
	Cannabis group		Cannabis group	
Early deviant behaviour	Non-users	Users	Non-users	Users
None	26,8 years (n = 24)	20,8 years (n = 26)	27,2 years (n = 33)	28,8 years (n = 10)
Mild	25,2 years (n = 27)	21,7 years (n = 26)	21,8 years (n = 23)	22,1 years (n = 4)
Severe	21,7 years (n = 33)	18,4 years (n = 23)	23,9 years (n = 20)	23,2 years (n = 7)

It can be seen that the group with the lowest mean age of criteria onset were male users of cannabis with severe early deviant behaviour (18,4 years). In males the difference between the mean age of criteria onset of users and non-users was more pronounced for all three behavioural groups than the corresponding differences in females. In the case of females no clear picture emerges, possibly due to the relatively small sample sizes.

Discussion

The cut-off point used in the Diagnostic Interview for Genetic Studies⁶ to determine cannabis abuse or dependency is more than 21 times a year. This is an arbitrary figure and the information obtained from subjects is not reliable. Who would be keeping an accurate record of the number of days they were using cannabis? On the other hand, clinicians treating schizophrenia subjects usually have a fair idea of who the subjects are that abuse cannabis. Of the male subjects in this database, 43,54% reported cannabis use/abuse as against 20,45% of females. This figure may be higher because cannabis use/abuse is usually underreported and the information collected from the subjects was not confirmed by urine analysis for cannabinoids. More males than females were heavy users. Looking at the figures in this database one can assume that approximately half of the male schizophrenia subjects and a quarter of the female schizophrenia subjects' used or abused cannabis. These figures are high and make cannabis use/abuse part of the management strategy of these subjects. Cannabis use/abuse must have an effect on factors such as the criteria age onset and the longitudinal course of the illness.

The longitudinal course of illness as classified by the DIGS⁶ can be applied only after at least one year has elapsed since the initial onset of the active-phase symptoms. If we refer to Table II of the results, the percentages are similar for the non-cannabis use/abuse group and the cannabis use/abuse group. The exception is the slightly higher percentage of cannabis users (45%) being classified as having a continuous course of illness than non-users (38%) and a slightly lower percentage of cannabis users with a single episode of psychosis with full remission (1%) versus non-users (5,4%). These differences are not significant. A higher percentage (14,1%) of non-cannabis use/abusers were never hospitalized compared to 8,8% of the cannabis use/abuse group. Although these findings are not statistically significant, they do point towards the fact that cannabis use/abuse may have a negative effect on the longitudinal course of the illness.

Information for early non-psychotic deviant behaviour was available for 207 subjects in the database. 60,7% (n = 207) reported one or more forms of early non-psychotic deviance. This was partly present (at least one form of early non-psychotic deviance) in 29,3% (n = 100), and strongly present (2 or more forms of early non-psychotic deviance) in 31,4% (n = 107). In a previous report the early non-psychotic deviant behaviour in Afrikaner and US patients with schizophrenia or schizoaffective disorder were compared and reported on.⁷ It was concluded that early non-psychotic childhood deviance in this independently collected Afrikaner population distinguished a distinct sub-type of patients and that the forms of early deviance manifested were meaningfully linked to the later outcome of the disease.⁷ The approach was based on retrospective reports of patients. This approach was not without its limitations but seemed useful to further explore patient-reported non-psychotic early deviant childhood behaviours.

In another comparative study of early non-psychotic deviant behaviour in the first ten years of life in Afrikaner patients with schizophrenia, schizoaffective disorder and bipolar disorder, it was found that the prevalence of early non-psychotic deviant behaviour was not significant in Afrikaner patients with bipolar disorder when compared to the other two diagnostic entities. The authors concluded that early non-psychotic deviant behaviour may therefore be used as a possible endophenotypic marker in schizophrenia and schizoaffective disorder, but not in bipolar disorder.⁸

The age at which a subject with schizophrenia first becomes psychotic is a variable trait relating to prognosis. An earlier onset of psychosis is associated with a more severe course, irrespective of the duration of the illness.⁹

The age of criteria onset being significantly different for males and females in this study corresponds to previous findings that the peak ages of onset are 15 to 25 years for men and 25 to 35 years for women.¹⁰

The results indicating a strong association between the use of cannabis and age at onset of psychosis in male schizophrenia patients match those of a study in Dutch male schizophrenia patients.⁹

Early deviant behaviour emerged as the most important factor in determining age of criteria onset in the present study, with the early deviant behaviour group having the oldest age of onset and the more severe group the youngest.

Although the interactive effect of substance use and early deviant behaviour is not significant in the model, there was a difference in the effect of early deviant behaviour between

cannabis users and non-users. In the group using cannabis there was no significant difference in age of criteria onset between those without and with early deviant behaviour, while in the non-user group the age of criteria onset of those with no early deviant behaviour was significantly older than that of those with severe early deviant behaviour. The mean age of criteria onset decreased with the severity of the deviant behaviour in both cannabis groups, with the non-users' mean age of criteria onset being consistently higher by at least one year compared to that of the cannabis users in all three behavioural groups.

Males with severe early deviant behaviour comprised the group with the youngest estimated mean age of criteria onset. These findings would add on to previous findings indicating that early deviance was linked to the later outcome of the disease.⁷ In the present study early deviance affected the age of onset of schizophrenia which is known to be associated with a more severe course of illness. These findings are significant in males with mild and severe, and females with severe early deviant behaviour.

Male users of cannabis with severe early deviant behaviour had the lowest mean age of criteria onset, namely 18,4 years. This can be interpreted that in males with a distinct subtype of schizophrenia (where early deviance is present) cannabis triggers the onset of a psychosis with a poor prognosis. These findings emphasize the importance of vulnerable male subjects abstaining from cannabis use.

Whilst previous findings from a study of Finnish families that the age at onset decreased as the family risk of schizophrenia increased¹¹, in this database family history of schizophrenia was less important in explaining the age of criteria onset than early deviant behaviour; the interaction of early deviant behaviour and male gender; and the interaction of cannabis use/abuse and male gender.

Limitations of study

Information on the use/abuse of cannabis obtained from the subjects may be unreliable, as it was not verified by urine analysis for cannabis. Had the subjects been admitted to the state psychiatric hospital, the investigators could have scrutinized clinical files where this information was available.

Information on early deviant behaviour was obtained from the subjects. This information was verified in a small percentage of subjects, and additional information was obtained from parents, as well as nursery school and early school records. This information may be inaccurate and biased. Information on early insults e.g. pregnancy history, perinatal and postnatal history, was obtained from subjects and parents, if possible. This information was not verified by obstetrician or hospital records.

The mean age at the time of DIGS interview was 34 years. This may have influenced the patients' recall of early deviant behaviour. Patients' current mental state may significantly have affected their report of past experiences. The mean age was verified with collateral information, wherever possible.

Conclusion

Although the figures are not directly comparable, it was found that the percentage of male and female Afrikaner schizophrenia subjects who used/abused cannabis was higher than the lifetime rates for males and females in a representative sample of grade 11 students in SA¹, which corresponds more or less to the figure reported by various substance treatment centres scattered

across South Africa, for cannabis as the primary drug of abuse.² More emphasis should be placed on the psycho-education and rehabilitation of young vulnerable individuals with schizophrenia who use and abuse cannabis.

Early deviant behaviour was the most important factor determining age of criteria onset and in male patients with schizophrenia may be a possible endophenotypic marker. The interactive effect of gender and cannabis use was also significant in explaining the age of criteria onset in males. Yet it seems that when cannabis is used, the effect of early deviant behaviour becomes less important in determining the age of criteria onset.

In our search for more sophisticated endophenotypes to aid the identification of susceptibility and modifying genes, early deviant behaviour, male gender and cannabis use/abuse in interaction may be factors to consider in future research.

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References

1. Parry CD, Myers B, Morojele NK, Flisher AJ, Bhana A, Donson H, Pludderman A. Trends in adolescent alcohol and other drug use: finding from three sentinel sites in South Africa. *J Adolesc.* 2001 27(4): 429-440.
2. South African Community Epidemiology Network on Drug use (SACENDU). *Monitoring Alcohol and Drug Abuse Trends in South Africa, SACENDU Research Brief, 2004; 7(1)* Available at <http://www.sahealthinfo.org/admodule/sacendu.htm>.
3. Verdoux, H. Cannabis and psychosis proneness. In: Castle D, Murray R eds, *Marijuana and Madness*. Cambridge: Cambridge University Press, 2004:75.
4. Karayiorgou M, Torrington M, Abecasis GR, Pretorius HW, Robertson B, Kaliski S, et al. Phenotypic characterization and genealogical tracing in an Afrikaner schizophrenia database. *Am J Med Genetics Part B (Neuropsychiatr Genet)* 2004; 124B: 20-28.
5. Abecasis GR, Burt RA, Hall D, Bochum S, Doheny KF, Lundy SL, et al. Genomewide scan in families with schizophrenia from the founder population of Afrikaners reveals evidence for linkage and uniparental disomy on chromosome 1. *Am J Human Genetics.* 2004; 74: 403-417.
6. Nurnberger JL, Blehar MC, Kaufmann CA, York-Cooler C, Simpson SG, Harkavy-Friedman J, et al. NIMH genetics initiative. Diagnostic interview for genetic studies, rationale, unique features, and training. *Arch Gen Psychiatry* 1994; 51: 949.
7. Sobin C, Roos JL, Pretorius HW, Lundy LS, Karayiorgou M. A comparison study of early non-psychotic deviant behaviour in Afrikaner and US patients with schizophrenia and schizoaffective disorder. *Psychiatry Res* 2003;117: 113-125.
8. Scholtz MC, Janse van Rensburg M, Roos JL, Pretorius HW, Levin JB. Early non-psychotic deviant behaviour as an endophenotypic marker in bipolar disorder, schizoaffective disorder and schizophrenia. *S Afr Psychiatry Rev* 2005:153-159.
9. Veen ND, Selten JP, Van der Tweel I, Feller WC, Hoek HW, Kahn RS. Cannabis use and age of onset of schizophrenia. *Am J Psychiatry* 2004;501-506.
10. Kaplan HI, Sadock BJ. *Synopsis of Psychiatry, 8th edition*, Baltimore: Lippincott, Williams and Wilkins 1998:475.
11. Suvisaari JM, Haukka J, Tanskanen A. Age at onset and outcome in schizophrenia are related to the degree of familial loading. *Br J Psychiatry* 1998;173 : 494-500.