Impact of Cannabis and Other Drugs on Age at Onset of Psychosis

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Objective: The aim of this study was to investigate the relationship between age and cannabis use in patients with a first psychotic episode, and to analyze the mediating effect of comorbid use of other drugs and sex on age at onset of psychosis.

Method: All consenting patients (aged 15 to 65 years) with a first psychotic episode needing inpatient psychiatric treatment during a 2-year period between February 1997 and January 1999 were considered, confirming a total of 131 patients. Subjects were interviewed using the Structured Clinical Interview for DSM-IV Axis I Disorders, and clinical and demographic data were collected. We used general linear models with age at onset as the response variable and survival Cox models to confirm the results. Both a multivariate linear model and the corresponding Cox model were fitted with a covariate that summarizes the most significant contributors that seemed to decrease age at onset.

Results: Regarding the effect of cannabis use, a significant gradual reduction on age at onset was found as dependence on cannabis increased, consisting in a decrement of 7, 8.5, and 12 years for users, abusers, and dependents, respectively, with respect to nonusers ($p = .004$, $p < .001$, and $p < .001$, respectively). Multivariate analysis showed a clear effect of cannabis use on age at onset, which was not explained by the use of other drugs or by gender. The finding was similar in the youngest patients, suggesting that this effect was not due to chance.

Conclusion: The major contribution of this investigation is the independent and strong link between cannabis use and early age at onset of psychosis, and the slight or nonexistent effect of sex and comorbid substance abuse in this variable. These results point to cannabis as a dangerous drug in young people at risk of developing psychosis.

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One of the most striking findings in recent years is the increased risk of developing psychosis and psychotic symptoms in cannabis users.[1] Indeed, the issue is still controversial.[2] The debate is open,[3] and there are unresolved questions regarding the measurement of psychotic symptoms, controlling for confounding factors, and the possibility of reverse causality.[2,4] One piece of supportive evidence is that some first-episode studies have found an earlier age at onset for individuals with a history of comorbid substance use, especially cannabis,[5–7] although not all studies have shown this.[8,9] One explanation for this possible link is that the illness is precipitated by substance use, although it remains uncertain whether this effect is limited to people with a predisposition to psychosis.[10,11] Another possible explanation is that

the early onset of symptoms is a risk factor for substance use. The experience of symptoms could make patients vulnerable to substance use, perhaps in an attempt to cope with the illness or to self-medicate.[4,12,13]

Some of the most contributing confounders can be the use of other drugs, as patients frequently abuse 2 or more drugs at the same time. Nevertheless, the most studied confounding factor that can mediate the association between age at onset and substance misuse is gender.[14–19] Substance misuse is more frequent in male patients, and age at onset has been reported to be earlier in men. Indeed, despite the numerous articles on the influence of gender in age at onset,[19] cannabis use was more important than sex in influencing age at onset in the research carried out by Veen et al.[7] The publication of those results gave rise to 2 letters.[3,20] One of them,[20] documenting a study that included a sample of patients diagnosed with chronic schizophrenia, showed that there was only a tendency to an association between age at onset of psychosis and cannabis use. The other strengthens the previous theories[21] considering that the link between male sex, early age at onset, and cannabis use could be due to the more common use of cannabis in young men.[3]

Drugs such as stimulants[22] and alcohol[6] have been reported to carry increased risk for the onset or the course of schizophrenia, bipolar disorder, and psychosis. In fact, abuse of at least 2 different drugs is quite frequent among young people, and this is especially true in patients with psychosis.[23] Indeed, in a sample of first-episode psychotic patients, those who abused alcohol and cannabis had an earlier age at onset and had poorer responses both to typical and atypical antipsychotics.[24] It has also been shown that heavy, but not mild, substance abuse is associated with poorer outcome in young psychotic patients[25] and that substance abuse remits in a small proportion of patients during the first year of the disease.[26]

We designed a study to investigate the relationship between age and cannabis use in patients with a first psychotic episode and to analyze the mediating effect of comorbid use of other drugs and gender on age at onset in this group of patients.

METHOD

Subjects

Data were gathered on first-episode psychotic patients consecutively admitted from February 1997 to January 1999 to a general hospital psychiatric ward in Vitoria, located in the Basque country. The hospital provides psychiatric care to all inhabitants (300,000) of the catchment area independently of their socioeconomic status. There is only 1 emergency room for psychiatric patients, and if necessary, patients are hospitalized in the psychiatric department of the general hospital, as there are no other hospitalization units (public or private) in the area. Therefore, the sample represents the whole psychotic population with a first psychotic episode needing inpatient psychiatric treatment. Patients were included in the study after informed consent to participate was obtained. Only 5 patients did not participate.

Assessments

First psychotic episode was defined as the first time a patient displayed positive psychotic symptoms of delusions or hallucinations. Subjects were aged 15 to 65 years and met *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) criteria for schizophreniform disorder, schizoaffective disorder, schizophrenia, delusional disorder, brief psychotic disorder, atypical psychosis, bipolar I and II disorder, or major depressive disorder with psychotic symptoms. Subjects with mental retardation, organic brain disorders, or drug abuse as a primary diagnosis were excluded. The DSM-IV Axis I diagnosis was made using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I).[27]

The day after admission, patients with first-onset psychotic symptoms were assessed with a protocol that included SCID-I and some relevant clinical and demographic variables, i.e., gender, age, and comorbidity with alcohol and drug abuse. The evaluations were performed during a clinical interview lasting about 90 minutes and pertaining to the previous week. The interview was carried out by 2 psychiatrists (A.M.G.-P. and I.R.) who had reached good interrater reliability for SCID-I diagnoses ($\kappa = 0.88$).

Using information from the patient, the key informant, the medical file, and drug screens, we determined whether the patient had used cannabis, how often the patient had used cannabis, and when this use had occurred. The research team discussed inconsistencies and selected the most reliable source. Cannabis use was defined as having taken cannabis at least once in the last month, and at least 4 times in the last year. Cannabis abuse and dependence were defined according to DSM-IV.

Additional information from clinical records, family informants, and staff observations were incorporated into the rating process. The patients were treated with medications as clinically appropriate. The ethical committee and the investigation commission of Santiago Apóstol Hospital approved the study.

Statistics

To provide the sample characteristics that summarize the type of patients analyzed, we used proportions for the categorical variables and median with interquartile ranges for the continuous ones. We also compared these sample characteristics between those who were cannabis users and those who were not by means of the χ^2 test or

Table 1. Descriptive Sample Characteristics of Patients With First Psychotic Episode and Comparisons Between Cannabis Users and Nonusers

Characteristic	Total (N = 131)	Cannabis Users (N = 67)	Nonusers (N = 64)	p Value (test)
Sex				.003 (χ^2)
Male	66 (87)[a]	61 (53)[b]	39 (34)[b]	
Female	34 (44)[a]	32 (14)[b]	68 (30)[b]	
Age group by sex				.0001 (Fisher)
Male, < 30 y	50 (66)[a]	70 (46)[b]	30 (20)[b]	
Female, < 30 y	18 (24)[a]	42 (10)[b]	58 (14)[b]	
Male, ≥ 30 y	16 (21)[a]	33 (7)[b]	67 (14)[b]	
Female, ≥ 30 y	15 (20)[a]	20 (4)[b]	80 (16)[b]	
Study level[c]				.561 (Fisher)
Elementary school	36 (47)[a]	51 (24)[b]	49 (23)[b]	
Middle school/ high school	49 (64)[a]	53 (34)[b]	47 (30)[b]	
University	14 (18)[a]	39 (7)[b]	61 (11)[b]	
Age at onset, y	25.8 (21.1–32.3)[d]	22.4 (20.3–26.3)[d]	29.3 (25.5–39.6)[d]	.001 (Mann-Whitney)
Days of hospitalization	18 (13–25)[d]	17 (11–24)[d]	20 (14–27)[d]	.061 (Mann-Whitney)

[a]Percentage of total with N in parentheses.
[b]Percentage of file with N in parentheses.
[c]Elementary school = ages 6 to 11; middle school/high school = ages 11 to 18; university = ages 18 and above.
[d]Median with interquartile range in parentheses.

the Fisher exact test (depending on the sample size) for categorical variables and using the Mann-Whitney test for continuous ones.

To evaluate the contribution of cannabis use and other drugs on age at onset of psychosis, we used general linear models with age at onset as the response variable. In addition, and taking advantage of the nature of this variable, survival Cox models were also used to confirm the results using time interval from birth to first psychotic episode as dependent variable. All analyses were carried out using the whole sample and also using the subgroup of younger patients (< 30 years) to corroborate the results.

Specifically, we analyzed the effect of cannabis (no use, use, abuse, or dependence) on age at onset, and also evaluated whether the number of drugs consumed and the use of other drugs had an effect on age at onset. Then we evaluated the individual contribution of each drug separately (cannabis, amphetamines, cocaine, methylenedioxymethamphetamine [MDMA, ecstasy], tobacco, and alcohol) to evaluate which drugs might also have an effect on age at onset. Afterward, these variables were included together with cannabis in the respective models to assess which of these variables had a mediating effect between cannabis use and age at onset. A variable was considered a significant mediator when the association between cannabis use and age at onset did not persist after the mediating variable was included in the model, whereas the association between the mediator and the outcome variable was statistically significant. Finally, both a multivariate linear model and the corresponding Cox model were fitted with a covariate summarizing the most significant contributors that seemed to diminish age at onset. Statistical analysis was performed using R, version 2.4.0 (available at http://www.r-project.org).

RESULTS

The sample characteristics of the patients are summarized in Table 1. There were twice as many males as females, and the proportion of cannabis users among males was significantly higher than among females, as expected.

Regarding the effect of cannabis use on age at onset (first group of rows in Table 2), there was a significant gradual reduction in estimates as the dependence on cannabis increased. The hazard ratios (HRs) were around 2, 3, and 7.5 for users, abusers, and dependents, respectively, compared to nonusers, which implies a decrease in age at onset of 7, 8.5, and 12 years, respectively (Figure 1A and 1B). This decreasing effect was also obtained when analyzing the group of youngest people (Table 2), thus corroborating the hypothesis that these results were not due to chance. To know whether the number of drugs used affects age at onset, we constructed the appropriate model, assuming that drugs consumed included cannabis, amphetamines, cocaine, and/or MDMA. The results (Table 2, Figure 1C and 1D) indicate that the crucial factor is to consume at least 1 drug. Indeed, consuming more than 1 had practically the same effect as consuming only 1. The HR was around 2 for users of 1 or 2 drugs and around 3 for users of 3 or more in both cases, when analyzing all patients and when restricting the analysis to the youngest. Finally, the results of the effect of consuming a drug other than cannabis showed a significant effect across the whole sample, but a doubtful effect on the youngest sample, suggesting that a multivariate model incorporating this information together with cannabis use would be advisable.

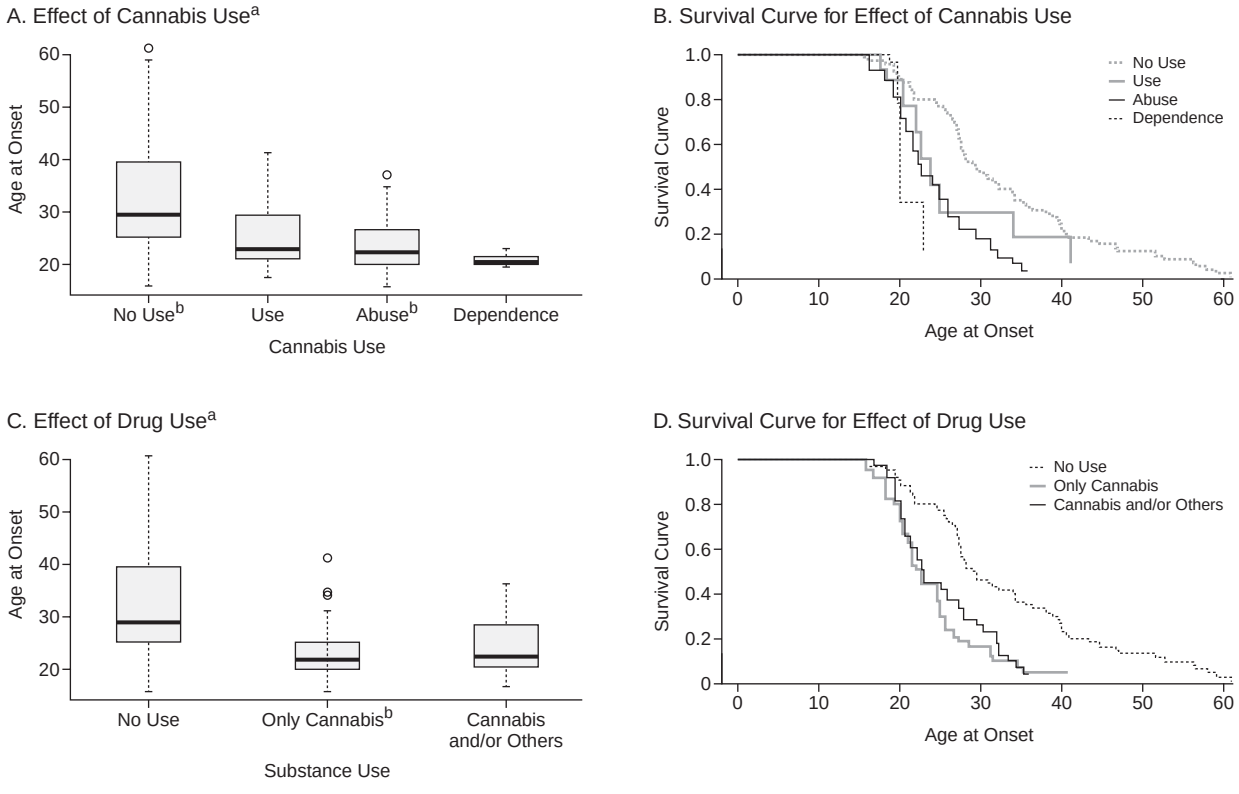
Regarding the individual contributions of each drug used (tobacco, alcohol, amphetamines, cocaine, and/or

Table 2. Linear Models and Cox Models for All Patients With a First Psychotic Episode and for Youngest

	All Patients				Only Patients < 30 Years Old			
	Linear Model		Cox Model		Linear Model		Cox Model	
Comparison	β	p Value	HR[a]	p Value	β	p Value	HR[b]	p Value
Age at onset vs cannabis use								
No use	32.66	< .001	1.00		24.35	< .001	1.00	
Use	–6.79	.043	2.05	.059	–2.45	.126	2.62	.037
Abuse	–8.68	< .001	3.04	< .001	–2.20	.008	1.97	.004
Dependence	–11.88	.010	7.46	< .001	–3.57	.063	3.90	.014
Age at onset vs no. of drugs								
No drugs	32.96	< .001	1.00		24.38	< .001	1.00	
1 drug	–8.70	< .001	2.84	< .001	–2.49	.007	2.21	.003
2 drugs	–7.96	< .001	2.62	< .001	–1.76	.088	1.68	.076
3 or more drugs	–10.01	.002	3.75	< .001	–2.94	.041	2.87	.011
Age at onset vs other drug use[c]								
No use	29.97	< .001	1.00		23.18	< .001	1.00	
Use	–4.54	.016	1.74	.007	–0.89	.293	1.36	.190

[a]Logrank test p value < .001, < .001, .007, respectively.
[b]Logrank test p value = .005, .008, .187, respectively.
[c]Category "other drug use" gathers data on amphetamines, cocaine, and/or MDMA use.
Abbreviations: HR = hazard ratio, MDMA = methylenedioxymethamphetamine.

Figure 1: Effects of Cannabis Use and Other Drug Use on Age at Onset of Psychosis and Corresponding Survival Curves



[a]Data presented as median (thick black line), interquartile range (grey box), and standard errors (bars).
[b]Datapoints above standard error bars represent atypical values.

Table 3. Multivariate Models for the Analysis of Possible Mediating Effects

	All Patients					Only Patients < 30 Years Old				
Model	B_{CU}[a]	p Value	B_M[b]	p Value	% Change[c]	B_{CU}[a]	p Value	B_M[b]	p Value	% Change[c]
Cannabis use	–8.651	< .001				–2.328	.003			
Cannabis use + gender	–7.917	< .001	–2.824	.096	–8.5	–2.042	.012	–1.223	.165	–12.2
Cannabis use + tobacco use	–7.440	< .001	–3.499	.091	–13.9	–2.582	.003	0.885	.450	10.9
Cannabis use + other drug use[d]	–8.512	< .001	–0.347	.857	–1.6	–3.068	< .001	1.407	.108	31.7
Cannabis use + alcohol use	–8.663	< .001	–8.663	.987	0.1	–2.397	.006	0.172	.849	2.9

[a]B_{CU} is the coefficient estimate for cannabis use.
[b]B_M is the coefficient estimate for the mediator variable.
[c]The percentage of change in the effect size (the coefficient estimate for cannabis use) when including the mediator.
[d]Other drugs are amphetamines, cocaine, and/or methylenedioxymethamphetamine (MDMA or ecstasy).

MDMA) on age at onset, we found that tobacco (log-rank test score = 10.6, p = .001, HR = 2.06), alcohol (log-rank test score = 5.5, p = .019, HR = 1.52), and amphetamines (log-rank test score = 8.88, p = .003, HR = 1.94) had an apparent significant effect, whereas cocaine (log-rank test score = 1.1, p = .303) and MDMA (log-rank test score = 3.7, p = .056) did not. However, these results should be considered with caution because of the possible presence of confounding factors. When including these variables in turn together with cannabis use to analyze the presence of mediating variables between cannabis use and age at onset, we found that none of these variables or gender could be considered as a mediating factor because none of them remained significant when including cannabis use, whereas cannabis use always remained significant (Table 3). Only gender and tobacco seemed to be close to significance (p = .096 and p = .091, respectively) in the whole sample, so these variables were candidates to be included in the multivariate model.

Finally, a multivariate analysis was carried out with the whole group of patients and the subgroup of youngest patients. A new variable was created incorporating the information obtained from the former analyses that included 5 categories regarding the use of drugs: no use of any kind of drug, use of only tobacco, use of only cannabis (and maybe tobacco), use of only other drugs (amphetamines and/or cocaine and/or MDMA, and maybe tobacco, but not cannabis), and use of cannabis and other drugs. This variable, together with gender, was included in the model, but gender was not significant. Given the lack of significance of 2 categories of this variable, we made categories focusing on no drug use, only cannabis use, and cannabis and/or other drug use. The results showed a clear effect of cannabis use on age at onset (HR = 3.1, p < .001), which was not augmented by the use of other drugs (HR = 2.6, p < .001). The same result was also obtained in the youngest patients (HR = 2.2, p = .003, and HR = 1.9, p = .018, respectively), suggesting that this result was not due to chance.

The clear effect of cannabis use on age at onset regardless of the use of other substances is also shown in Figure 1.

DISCUSSION

We assessed the independent contribution of sex, cannabis use, and comorbid use of other drugs on age at onset of psychosis in a cohort of patients in Vitoria, Spain. The interaction of these 3 factors has only rarely been studied before.[28] The strong link found between cannabis and early age at onset after considering the other variables establishes cannabis as a dangerous drug, especially in young people. Also relevant is the only slight or nonexistent effect of sex and comorbid substance abuse on age at onset of psychosis. The interaction of age, sex, and cannabis use was previously studied without considering other drugs.[7] Our findings are in line with others that have been the subject of much discussion.[3,20] Men clearly had an earlier age at onset than women, with a difference of 5 years, in agreement with all previous reports. Nevertheless, and as found by Veen et al.,[7] the effect of cannabis is much greater, with a difference of almost 12 years in those with greater use of cannabis. When considering the effect of both use of cannabis and gender together, only cannabis remained significant, so the reason for the earlier onset in males could be that males use drugs more frequently than females, although the p value for gender was close to significance (p = .096).

Some of the possible factors affecting age at onset that we assessed may be strongly age-related, such as cannabis use and alcohol abuse, and these factors could produce a bias in the results.[3] Hence, we readjusted all our models by using a subsample that represented the youngest patients but that allowed reasonably powerful tests at the same time. All the results pointed in the same direction, so the association was scarcely due to chance. Therefore, we definitively agree with Veen et al.[7] about the importance of cannabis, but not gender, as an independent factor contributing to earlier onset of psychosis. Moreover, the results are not in line with the hypothesis that cannabis use and age at onset are related just because younger patients are more prone to using cannabis. If this were the case, differences would not be found in the youngest sample. Moreover, the inverse dose relationship

of cannabis with age found in our study and in others[4,28,29] gives more strength to the causal or to the effect modification hypothesis (development of psychosis in people susceptible) discussed in previous studies of the general population.[2,11] Our results point to younger ages at onset in heavy smokers with HR ranges from 2 in users of cannabis to 3 in abusers and 7.5 in dependents. It is clear that heavy use has a different effect both on age at onset[2] and, as established previously, on outcome.[25]

Regarding other factors that could have an influence on age at onset and therefore act as confounders,[28] it seems that none of those considered here (tobacco, amphetamines, cocaine, and alcohol) had enough influence to remain significant when cannabis use was considered, and therefore none of them could have a mediating effect on the association of cannabis use and age at onset. Only tobacco was close to significance ($p = .091$), a finding not in line with that of Zammit et al.,[30] who found that smoking may protect against developing schizophrenia. Indeed, there was a strong association in our sample between cannabis use and tobacco smoking, and smokers were in general younger than nonsmokers. The slight effect of smoking on age at onset found in a previous study was related with the neuroprotective effects of nicotine and the differential release effects of nicotine in the prefrontal cortex.[30–33]

Taken together, our findings suggest a firm relationship between cannabis use and early onset of psychosis, while the weight of other drugs is slight or nonexistent. Thus other variables such as alcohol abuse or use of stronger drugs such as cocaine do not have a significant effect on the response variable and cannot be considered as mediating variables because, when included in the model, they do not remain significant, in contrast to cannabis use. Finally, all these results were confirmed with the use of a subsample of younger patients (< 30 years old).

This association cannot be explained by chance and is dose related. Like other types of study, epidemiologic and clinical studies have some limitations and uncertainties, including difficulties in showing causal relationships. Nevertheless, these limitations do not preclude any firm conclusion from being drawn.

The present results were found in a well-defined catchment area located in the South of Europe, and the sample represents first-episode psychosis within the area. However, age at onset of psychosis is not exactly the same in all countries and latitudes, and the same can be said with regard to drug abuse. Drugs used 20 years ago were different, which might explain different results in relation to the effect of gender on the onset of psychosis.[14] It is also important to remember that samples of chronically ill patients with schizophrenia who experienced their first symptoms some decades ago might be somewhat different from present groups. Finally, first-episode psychotic patients are not only patients with schizophrenia, as defined by the DSM-IV criteria,[34] but also include patients with other diagnoses. For instance, an association between early age at onset, poor outcome, and cannabis use has also been suggested in studies on patients with mood disorders[34] and, particularly, mania.[35–38]

The clinical importance of this finding is potentially high: cannabis use is extremely prevalent among young people, and although some drug use is not so prevalent (but is on the increase, such as cocaine use), other drugs are especially frequent, such as tobacco and alcohol. Estimates of the attributable risk suggest that the use of cannabis accounts for about 10% of cases of psychosis. As Fergusson stated,[2] the task of deciding the harmful effects of cannabis involves a "choice of evils" in which the rights of the majority who use cannabis, apparently without experiencing problems, are balanced against the risks of a minority who may develop serious health consequences.[39] We need to develop an informed consensus on the risks posed by cannabis and the mechanisms for dealing with such risks.

This investigation has several strengths. The most important is that the sample is population-based. Other strengths include the following: diagnosis was made by 2 independent researchers, a key informant and the patient were consulted, and the medical records of all patients were available, including information from the emergency room.

It also has some limitations: all patients were hospitalized, and although the great majority of first-episode psychotic patients were included in the sample, a small proportion of patients (i.e., outpatients and those who chose not to participate) did not take part in the research. Furthermore, all patients were treated with antipsychotic medication. However, the main limitation of this study was the difficulty of controlling the probability of being a cannabis user, something that changes from one period to another, and which can contribute to variations in the risk of developing early psychosis. The probability of being a cannabis user has increased among young people in the last 20 years according to the Spanish Government.[40] To offset this problem, we repeated the analysis in the subsample of still young people (< 30 years), as this is the group of people for whom the use of cannabis has become a socially acceptable and frequent habit. An alternative and more rigorous way to avoid this problem could have been to make use of age-period-cohort models, which would make it possible to relate the evolution of cannabis users with age at onset of disease but also taking into account both the effect of the time period of illness onset and the corresponding birth-cohort effect. Owing to the short period considered and the relatively small sample size in this study, it was not possible to carry out this analysis, but this article may be considered as a starting

point for revealing the effects of cannabis use on age at onset of psychosis. Age-period-cohort models are proposed here as a statistical tool for future research in this direction.

In conclusion, a strong relationship was found between cannabis use and early age at onset of psychosis after considering other variables, and this relationship establishes cannabis as a dangerous drug for young people at risk. Interestingly, the effect of gender and comorbid substance abuse on age at onset of psychosis was either only slight or nonexistent.

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