Revisión

Factors associated with the onset of cannabis use: a systematic review of cohort studies

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(Factores asociados al inicio del consumo de cannabis: una revisión sistemática de estudios de cohortes)

Abstract

Objective: To determine the factors associated with the onset of cannabis use through a systematic review of cohort studies.

Methods: An internet-based search was performed using several keywords and their combinations. Original studies with longitudinal design and the onset of cannabis use as dependent variable, as well as review studies were included, published between January 1980 and May 2004. Methodology quality of the studies was assessed independently by two reviewers, according to pre-established criteria, in order to classify studies in high, mid or low quality. Agreement between reviewers was assessed through kappa coefficient.

Results: A total of 32 relevant studies were identified, of which 13 were of higher quality. Selection bias for the inclusion of consumers at the baseline measurement and lack or insufficient adjustment for confounders were the causes of exclusion. The factors of great evidence related to the onset of cannabis use were masculine sex, consumption of tobacco or alcohol, having a problematic relationship with parents, and cannabis consumption by friends.

Conclusion: Results highlight the importance of different individual, family and environmental factors on the onset of cannabis use. These must be considered to properly arrange intervention programs focusing on primary prevention among teenagers.

Keywords: Cannabis. Systematic review. Longitudinal studies.

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Introduction

The consumption of cannabis has various consequences for human health at the physiological, social and psychological levels. Although relatively few studies have systematically assessed the impact of cannabis on human health, the use of cannabis has been associated with cases of bronchitis, chronic cough and pre-cancerous alterations in the pulmonary tissue.
use of cannabis interferes with the normal workings of complex functions such as memory, concentration and learning, can cause a reduction in the educational achievement of teenagers, exacerbates psychosis and increases the risk of traffic accidents.

Cannabis is the most frequently consumed illicit drug in most developed countries. In Europe as a whole, it is estimated that at least one in five adults has consumed cannabis at some time in their life. Furthermore, in recent years there has been a noticeable increase in cannabis consumption amongst teenagers and young adults. In 2003, 29.0% of the Spanish population aged between 15 and 64 admitted to having consumed cannabis at some time in their life, while in young people aged between 15 and 29 this percentage rose to 35.9%.

Knowledge of the factors associated with the onset of cannabis consumption is essential for designing and implementing prevention programs aimed at teenagers and young adults. Although various authors have previously reviewed factors associated with the consumption of cannabis and other illicit drugs, such reviews have generally been rather unsystematic. They have been fundamentally based on cross-sectional studies and have tended not to exclude studies containing significant methodological limitations.

The aim of this work was to determine the factors associated with the onset of cannabis consumption by means of a systematic review of cohort studies.

Methods

An internet-based bibliographical search was carried out consulting Medline, Cochrane Library, ISI data bases, Documed, PsycINFO, PsyARTICLES and various thesis data bases (Teseo and the data bases of various universities). The following key words and their combinations were used: “cannabis”, “marihuana”, “associated factors”, “related factors”, “predictive factors”, “determinants”, “adolescents”, “students”, “youth”, “school”, “longitudinal”, “follow-up”, and “prospective”. The selection criteria for the study established that references should be original articles published between January 1980 and May 2004, in English, Spanish, French, Italian or Portuguese, that they should be empirical, involve cohort studies and consider the onset of cannabis consumption as a dependent variable. The total number of articles was completed with the addition of other references from articles selected as a result of the internet search. Reviews were also used to help locate further original sources. All of the authors agreed with this search strategy.

Two of the authors (MG and DO) carried out a critical review of the studies, basing their decisions on the following criteria: sample size and representativity; average age at the beginning of the study and average age at the onset of cannabis use; length of follow-up; clear definition of exposure and outcome and valid method of assessment; conclusions supported by results that also considered potential sources of bias and limitations; level of adjustment for potential confounders; and with the onset of cannabis use as a dependent variable, having excluded from the analysis subjects who were consumers of cannabis at the onset of the monitoring period. These last 3 criteria were used to define the methodological quality of the studies. The reviewers independently assessed the articles and assigned them to one of three quality categories: high, medium or low. When discrepancies arose, a third reviewer (CA) analyzed the article in question and made an independent decision. The degree of concordance between the reviewers was measured using the kappa coefficient.

Only studies that were judged to be of methodologically high quality were selected to determine the factors associated with the onset of cannabis use. The factors identified were grouped into a smaller number of dimensions on the basis of conceptual similarity in order to render the final analysis more operative (table 1).

Of the 13 studies finally selected as being of high quality, 8 used Odds Ratios (OR) as a measure of association. Most of these studies showed a 95% confidence interval (CI), but in some only the p-value was provided. In one study, survival analysis was carried out and Hazard Ratios (HR) were used to measure association with a 95% confidence interval. Three of the 13 studies selected employed multivariate hierarchical models and used the coefficient of determination to estimate the level of association. All of the factors analyzed in 2 or more studies that employed either OR or HR as a measure of association are presented in figure 1. In one of these studies, the results were analyzed for a single sample of pupils but have been presented after stratification into different age groups. These results were treated as a single study and we selected the largest OR for each factor.

Results

We identified 33 articles that met the selection criteria, and which corresponded to 32 different studies. Two articles presented results from the same study and so the one that presented the more preliminary results was discarded. Very few articles discussed the question of bias and methodological limitations. This parameter could not therefore be used to discriminate between the quality of different studies and was consequently rejected as a criterion for study quality. Of the 32 studies selected, 13 were classified as being of...
Table 1. Range of factors associated with the onset of cannabis consumption identified in the 13 studies selected as being of high methodological quality and grouped by similarity

<table>
<thead>
<tr>
<th>Type of variable</th>
<th>Definition of the same variable in the selected studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Socio-demographic variables</td>
<td></td>
</tr>
<tr>
<td>Low socio-economic status</td>
<td>Family social position (poorly educated parents, low occupational status, young mother, Maori/Pacific Island parentage (vs. European parentage), single parent family (vs. two parent family), socio-economic disadvantages (low socio-economic status, young mother at age of first pregnancy, low level of mother education, single parenting) (vs. two parent family), low socio-economic status (education and parents’ profession))</td>
</tr>
<tr>
<td>Availability of drugs in local setting</td>
<td>High level of weekly cannabis use in school at study inception; availability of drugs</td>
</tr>
<tr>
<td>Consumption variables</td>
<td></td>
</tr>
<tr>
<td>Tobacco consumption</td>
<td>Daily tobacco consumption; current tobacco consumption; onset of tobacco consumption before the age of 15; consumption of legal drugs; regularly tobacco consumption</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>Alcohol consumption; regular alcohol consumption; high alcohol consumption; consumption more than 2 days a week or of high doses; consumption of legal drugs</td>
</tr>
<tr>
<td>Individual variables</td>
<td></td>
</tr>
<tr>
<td>Antisocial conduct</td>
<td>Behavioural disorder (according to DSM-IV); antisocial problems reported by parents and teachers (according to Rutter-Child Scales A and B); Antisocial behaviours (property damage; vandalism; car damage; making money); interpersonal conflicts (fighting, carrying weapons, running away from home, requisition from school); theft (stealing property from parents, or other, stealing cars)</td>
</tr>
<tr>
<td>Psychiatric morbidity</td>
<td>Psychiatric morbidity (according to CIS-R [Clinical Interview Schedule], poor mental health (according to General Health Questionnaires [Goldberg, 1972]); behavioural inhibition during childhood (the); mental disorders (somatormorphic and alimentary)</td>
</tr>
<tr>
<td>Personality</td>
<td>Adolescent personality (attitude towards perversion/diversion, low educational expectations, low expectations of academic recognition, low Marlowe Crowne Index), non-conventional personality (deviance, rebelliousness, sensation seeking, tolerance of deviance), non-conventional personality</td>
</tr>
<tr>
<td>Family and friend variables</td>
<td></td>
</tr>
<tr>
<td>Single parent families</td>
<td>Divorced/separated parents (vs. reared with both parents); change of parents</td>
</tr>
<tr>
<td>Parental factors</td>
<td>Poorly functioning family (parental monitoring, rules, discipline and reward practices); parental factors (warmth, identification, permissiveness, discipline and legal drug, marijuana or illicit drug use by the parents)</td>
</tr>
<tr>
<td>Cannabis use by friends</td>
<td>Use and possession of marijuana by friends and friends with a favorable attitude towards cannabis and alcohol use; cannabis use by a number of friends; cannabis use by acquaintances; drug use by friends; marijuana use by friends</td>
</tr>
</tbody>
</table>

high methodological quality (table 2). Three of the 13 studies had oversampled populations with either low socio-economic levels or a high prevalence of the consumption of addictive substances. The main limitations identified in the 19 studies judged to be of medium or low methodological quality were: selection bias, as they did not exclude people who were already cannabis consumers at the onset of the cohort monitoring period; and the lack of adjustment for potential confounders presenting results obtained from bivariate analyses. The degree of concordance between the reviewers measured by the kappa coefficient was 0.65. The 13 studies included in this review operatively defined the “onset of cannabis use” on the basis of lifetime cannabis consumption. Seven of these 13 studies defined this use on the basis of questions such as “Have...
you ever smoked marijuana?", which had two possible answers: ‘never’ or ‘at some time’. Six of the 13 studies defined it from questions relating to frequency of use, such as “How often have you smoked marijuana?". For the purposes of analysis, these studies classified the replies in terms of ‘never’ vs. ‘whatever consumption frequency’. Two of these 6 studies explored past consumption, with one examining the pre-

![Figure 1. Factors associated with the onset of cannabis consumption identified in 10 of the 13 studies judged to be of high methodological quality.](image)

<table>
<thead>
<tr>
<th>Social-demographic variables</th>
<th>Consumption variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEX (M/F)</td>
<td>2.6 [1.2-5.4]</td>
</tr>
<tr>
<td>Age</td>
<td>1.7 [1.1-2.6]</td>
</tr>
<tr>
<td>Educational attainment</td>
<td>1.3 [0.9-1.8]</td>
</tr>
<tr>
<td>Occupation</td>
<td>1.1 [0.7-1.6]</td>
</tr>
<tr>
<td>Antisocial behavior</td>
<td>1.7 [1.1-2.7]</td>
</tr>
<tr>
<td>Family and friend variables</td>
<td>0.8 [0.5-1.2]</td>
</tr>
</tbody>
</table>

In one of these studies, it was only possible to chart a single factor, which was seen as the most interesting with respect to the aims of that particular study, while the only information provided for the other factors was their respective degree of significance. In 3 of the studies the association between the different variables was measured by a means other than either Odds Ratio or Hazard Ratio (see text). This study uses Hazard Ratio as a measure of association rather than Odds Ratio. No confidence intervals, but statistically significant.

OR: Odds Ratio; 95% CI: 95% Confidence Interval.
vious year and the other focusing on the previous 6 months19-21. We decided to include these studies because cannabis consumption by adolescents at some time in the past year and at some time in the past six months showed a close correlation with consumption at some time in the individual’s life.

Figure 1 shows the factors associated with the onset of cannabis consumption identified in 10 of the 13 studies judged to be of high methodological quality. In one of these studies, it was only possible to chart a single factor, which was seen as the most interesting with respect to the aims of that particular study, while the only information provided for the other factors was their respective degree of significance11. Of these factors, low socio-economic status and poor relations with parents were the factors that were significantly associated with the onset of cannabis use. No statistically significant association was observed with either coming from a single parent family, having moved home, having an emotionally sensitive mother, or avoiding punishment.

In the 3 studies that could not be charted, the factors identified and significantly associated with the onset of cannabis consumption were: female sex 27, age 256.

<table>
<thead>
<tr>
<th>Main author</th>
<th>Year</th>
<th>City (country)</th>
<th>Years monitoring</th>
<th>n</th>
<th>Mean age at initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guxens M et al.</td>
<td>2007</td>
<td>New York (USA)</td>
<td>3</td>
<td>234</td>
<td>15.5</td>
</tr>
<tr>
<td>Bailey</td>
<td>1990</td>
<td>South-east states (USA)</td>
<td>1.5</td>
<td>3,454</td>
<td>11-15</td>
</tr>
<tr>
<td>Pederson</td>
<td>1990</td>
<td>Oslo area (Norway)</td>
<td>1.6</td>
<td>1,230</td>
<td>17.5</td>
</tr>
<tr>
<td>Hammer</td>
<td>1991</td>
<td>(Norway)</td>
<td>2</td>
<td>343</td>
<td>17-20</td>
</tr>
<tr>
<td>Ferguson</td>
<td>1993</td>
<td>Christchurch (New Zealand)</td>
<td>15</td>
<td>675</td>
<td>0</td>
</tr>
<tr>
<td>Andrews</td>
<td>1993</td>
<td>Urban areas in the south-west of Oregon (USA)</td>
<td>2</td>
<td>646</td>
<td>13.2</td>
</tr>
<tr>
<td>Broek</td>
<td>1999</td>
<td>Two cities in the state of New York (USA)</td>
<td>13</td>
<td>481</td>
<td>13</td>
</tr>
<tr>
<td>Akren</td>
<td>2000</td>
<td>(USA)</td>
<td>10</td>
<td>3,336</td>
<td>14-21</td>
</tr>
<tr>
<td>Covey</td>
<td>2000</td>
<td>Victoria State (Australia)</td>
<td>3</td>
<td>1,347</td>
<td>14.5</td>
</tr>
<tr>
<td>Kosterman</td>
<td>2000</td>
<td>Seattle (USA)</td>
<td>7.5</td>
<td>787</td>
<td>10.8</td>
</tr>
<tr>
<td>McGee</td>
<td>2000</td>
<td>New Zealand, Māori and Pacific Islands (New Zealand)</td>
<td>15</td>
<td>691</td>
<td>3</td>
</tr>
<tr>
<td>Montijo</td>
<td>2001</td>
<td>Brooklyn, Nueva York (USA)</td>
<td>3</td>
<td>399</td>
<td>16.7</td>
</tr>
<tr>
<td>Von Sydow</td>
<td>2002</td>
<td>Munich (Germany)</td>
<td>4</td>
<td>1,717</td>
<td>17.7</td>
</tr>
</tbody>
</table>

*Age range at onset of use, the average not being available in the article; estimation of the average age depending on the sampling method: those who were 14-15 years old were sampled with twice the probability of those who were 16-21, and those who were 22-24 years old were sampled with half the probability, USA = United States of America.
(great age, greater use)\textsuperscript{22}, low socio-economic status\textsuperscript{14}, belonging to a single parent family\textsuperscript{17,22}, forming part of a problem family\textsuperscript{17,22}, suffering the effects of strong parental discipline\textsuperscript{25}, individual personality\textsuperscript{23,26} and having a cannabis consuming father\textsuperscript{22}. In contrast, the factors that were identified but not significantly associated with the onset of cannabis consumption were: drug consumption by the individual him/herself\textsuperscript{15}; cannabis consumption by friends\textsuperscript{22} and tobacco and alcohol consumption by the individual’s father and mother\textsuperscript{22}. Factors that were analysed in isolated studies (not represented in figure 1) and which had a significant association with cannabis consumption include: going to church (OR = 0.73; 95% CI, 0.56-0.94)\textsuperscript{24}; belonging to a problem family (OR = 1.22; 95% CI, 1.01-1.47)\textsuperscript{15}; intending to consume drugs in the future (OR = 2.8; 95% CI, 2.7-5.4)\textsuperscript{24}; having a “non-conventional” personality (OR = 1.32; 95% CI, 1.01-1.75)\textsuperscript{24}; suffering psychological problems (OR = 1.08; 95% CI, 1.01-1.10)\textsuperscript{24}; exhibiting socially conflictive behaviour and rejecting conventional norms (OR=1.75; 95% CI, 1.17-1.47)\textsuperscript{24}; following rules against the consumption of cannabis (HR = 0.64; 95% CI, 0.46-0.81)\textsuperscript{24}; being subjected to strict parental discipline (HR = 0.75; 95% CI, 0.53-0.96)\textsuperscript{24}; and having siblings who consume alcohol (OR = 1.45; 95% CI, 1.01-2.12)\textsuperscript{24} or cannabis (HR = 1.48; 95% CI, 1.36-1.60)\textsuperscript{24}. Three studies from the United States explored the variable “belonging to a particular race/ethnicity” without obtaining any conclusive results\textsuperscript{22,25,30}.

**Discussion**

As far as we know, this is the only systematic review of cohort studies that has aimed to identify the factors associated with the onset of cannabis consumption. A review of longitudinal studies makes it possible to identify independent risk factors that can help predict the onset of cannabis consumption and which play a causal role in, or are otherwise associated with, the onset of cannabis consumption. As tends to occur in cases of behaviour exhibiting a complex and multi-factorial etiology, the studies identify a wide range of risk factors which include many different aspects. These include factors relating to social and family circumstance or educational performance and other factors such as the availability of drugs in the immediate environment, the behavioural models of parents and—above all—friends, and other psychological pathologies or sources of conflictive behaviour. However, the factors identified that seem to merit particular attention on account of their frequent appearance in a large number of studies are: male sex\textsuperscript{17,21,23,25,26}, the consumption of tobacco\textsuperscript{17,21,23,26} and alcohol\textsuperscript{17,21,23,25}, problematic relations with parents\textsuperscript{17,21,23,26} and cannabis consumption by friends\textsuperscript{17,21,24,30}.

In most studies\textsuperscript{17,22,24,25,26}, it was observed that boys had a greater risk of becoming cannabis consumers than girls. Even so, some studies\textsuperscript{17,22} reported a greater incidence of consumption among girls, especially before the age of 21\textsuperscript{18}, as well as a greater degree of dependence amongst female consumers. In another study\textsuperscript{23}, an association was observed between cannabis consumption by mothers and the onset of consumption by their daughters. Whatever the case, beyond any specific mechanisms that may explain part of these differences, the influence of gender should be evaluated in the light of the consumption tendencies described in several recent studies\textsuperscript{29}. In our setting, recent years have seen a certain convergence in the indicators relating to the consumption of tobacco, alcohol and cannabis by teenagers. Several studies carried out in the United States show that the differences observed in the prevalence of drug consumption between the two sexes could be largely due to differences in opportunities for consumption, rather than to differences in the probability of consuming for the first time when an opportunity presents itself\textsuperscript{28,51}. This suggests that the greater cannabis consumption observed amongst boys could be explained by the fact that they tend to have more opportunities to start consuming the drug than girls; when girls have the same opportunities they exhibit the same probability of consuming cannabis.

Kandel et al\textsuperscript{22} have presented a stepping-stone model for drug consumption which is currently subject to discussion. This model is based on a putative progression in consumption, which starts with legal drugs such as tobacco and alcohol. According to these authors, this would facilitate the consumption of marihuana, which—in turn—would subsequently act as a gateway to the consumption of other illegal and psychoactive drugs. In this review, the consumption of alcohol and tobacco both appear as factors associated with the consumption of cannabis, which would tend to confirm the stepping-stone model\textsuperscript{17,21-23,54}, at least with regard to the increased risk of cannabis consumption amongst the consumers of legalised drugs. This association could be due to the form of consumption, in the case of tobacco, and to the search for immediate effects, in the case of alcohol, in addition to other common mechanisms such as the symbolic nature of transgression and socialising aspects of consumption. The stepping-stone consumption model has, however, been questioned in some studies\textsuperscript{19,27} that showed that cannabis consumption was a factor associated with the onset of tobacco consumption. This could be explained by the fact that in environments in which the consumption of cannabis is very prevalent, it is possible to observe the onset of cannabis consumption previous to that of tobacco amongst some young adults. Other authors suggest that the consumption of tobacco, alcohol and cannabis may start at the same time, because the
determining factors associated initiation are common to all three drugs. Moreover, in another study referred to in this review, the use of other illegal and psychoactive drugs was also signalled as a factor associated with initiation in the use of cannabis. This was probably due, at least in part, to the fact that the study in question focused on a population with a low socio-economic level and a high prevalence of drug abuse. In such cases, it has been suggested that the populations in question exhibit a different pattern of use from the rest of the population and that the risk factors associated with initiation in the use of drugs are different, although any such differences could be fundamentally due to environmental conditions such as the availability of drugs in the local setting.

Another relevant factor is the presence of friends who use drugs. This factor encompasses the importance of having good and harmonious communication with parents, the ability to establish such communication, and also concerns the relationship between mother and child and the interaction between children and their parents and how the former identify with the latter. The importance of the parental role model is demonstrated within the range of social influences. A bad child-parent relationship implies the elimination of the passive model as a protective factor. It also implies the loss of the subjective norm, which is what prompts adolescents to adjust their behaviour in accordance with the position of relevant figures within their social environment, such as—in this case—theirs parents. The existence of a good, close parent-child relationship tends to favour the development of self-regulatory mechanisms and more effective social abilities.

Cannabis use by peers is signed as another important factor in the initiation of its use by young people. The role of friends has, however, been the subject of much argument in recent years. Several authors have suggested that it is more a matter of peer selection than of peer pressure. Whatever the case, these would no doubt be interrelated phenomena, and it should be stressed that in the present review this factor appeared amongst the most important factors for a wide age range; for young people aged between 14 and 26.

The availability of drugs in the local setting appears to be a factor of average importance. It would, however, seem more credible if it were a factor of major importance as it is an accessibility factor, and is seen as a key facilitating factor in the PRECEDE model. This average rating could be due to the fact that this variable was not taken into account in all of the studies. As far as the methodological limitations of this study are concerned, it should first be stressed that the review process was subject to publication bias, as the search was only conducted using free search engines and we only selected articles published in English, Spanish, French, Italian or Portuguese. Another important limitation was the fact that the same factors were not analysed in all of the studies considered. As seen in table 1, there were different approximations to the same dimension in the different studies selected. In the studies that examined the use of drugs and different types of conduct, the diversity of potentially related factors made it difficult to consider all of the variables in each study. If a factor was only identified in a single study, it could mean that it was less important than others or that it had simply not been investigated in other studies. It should also be remembered that in these studies the variables were gathered by means of self-administered questionnaires or interviews and may therefore have been subject to information bias due to the limited validity of some responses.

It is also appropriate to point out that previously published reviews relating to factors associated with drug use were not systematic; they included cross-sectional studies and did not exclude studies of low methodological quality, such as studies whose results were not adjusted for potential confounders. Moreover, these reviews did not focus their attention on the onset of drug use but rather on the use of drugs themselves, without differentiating between incident and prevalent use. Furthermore, these other reviews included the use of alcohol as well as that of cannabis and other illegal drugs.

Models that analyse behaviour are not determinant causal models. Above all, this type of study helps to define risk patterns which tend to favour certain types of conduct. The predictive factors that have been identified in this review are principally social and psychological in nature. In consequence, preventative measures should focus on increasing the awareness of adolescents of the social influences that could lead them to consume cannabis and also on providing them with the tools with which to face up to such situations. It is also important to educate young people in values and beliefs related to drug use and, at the same time, to introduce preventive measures to discourage the use of tobacco and alcohol. Botvin’s Life Skills Training model has helped to reduce the consumption of addictive substances, as well as provoking a change in behaviour with respect to drugs. It therefore provides an initial sign that primary prevention of cannabis use in this age group is possible. Such programs also need to include components that are directed towards parents in order to strengthen relations between adolescents and their parents. In doing this, they should also help to prevent the consumption of drugs.

In conclusion, the factors associated with the onset of cannabis consumption tend to relate to: the individual, including such considerations as age, sex, poor academic achievement, legal drug use and antisocial conduct; the family, with factors such as the level of communication between parents and children and relations
within the family, family problems, belonging to a single parent family, and strict parental discipline; and environmental factors, such as the influence of friends; the consumption of cannabis by friends and the availability of drugs in the local setting. These factors should all be taken into account when developing strategies aimed at preventing the consumption of cannabis by adolescents and young people.

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References


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