Attention deficit hyperactivity disorder symptoms and cannabis use after one year among students of the i-Share cohort

Short title: ADHD and frequency of cannabis use

François Arnaud Matthieu Jean, MD MS[1-3]
Julie Arsandaux, MS[2,3]
Ilaria Montagni, PhD[2,3]
Ophélie Collet, Msc[2,3]
Mélina Fatséas, MD PhD[2,4-6]
Marc Auriacombe, MD PhD[2,4,5,7]
Josep Antoni Ramos-Quiroga, MD PhD[8-11]
Sylvana M. Côté, PhD [2,3,12]
Christophe Tzourio, MD PhD[2,3,5]
Cédric Galéra, MD PhD[2-5]

[1] Dr Jean Eric Techer Hospital, Department of Psychiatry, Calais, France
[2] University of Bordeaux, Bordeaux, France
[3] National Institute of Health and Medical Research (Institut national de la santé et de la recherche médicale - INSERM), Bordeaux Population Heltch Research Center, UMR1219, HEALTHY Team, Bordeaux, France
[4] Charles Perrens Hospital, Bordeaux, France
[5] Centre Hospitalier Universitaire de Bordeaux (CHU de Bordeaux), Bordeaux, France
[6] National Center for Scientific Research (Centre national de la recherche scientifique - CNRS), CNRS-UMR 5287- Institut de Neurosciences Cognitives et Intégratives d'Aquitaine (INCIA), Bordeaux, France
[7] National Center for Scientific Research (Centre national de la recherche scientifique - CNRS), Addiction Team/SANPSY, USR 3413, Bordeaux, France
[8] Group of Psychiatry, Mental Health and Addiction, Vall d'Hebron Research Institute (VHIR), Barcelona, Spain
[9] Hospital Universitari Vall d'Hebron, Department of Psychiatry, Barcelona, Spain
[10] Biomedical Network Research Centre on Mental Health (CIBERSAM), Instituto de Salud Carlos III, Barcelona, Spain

This peer-reviewed article has been accepted for publication but not yet copyedited or typeset, and so may be subject to change during the production process. The article is considered published and may be cited using its DOI.

[11] Universitat Autònoma de Barcelona, Department of Psychiatry and Legal Medicine, Barcelona, Spain
[12] University of Montreal, Canada

Corresponding Author
Pr Cédric Galéra
Pôle universitaire de psychiatrie de l'enfant et de l'adolescent
Centre hospitalier Charles-Perrens, 146bis, rue Léo-Saignat, 33076 Bordeaux, France
Tel: 0033.5.56.56.17.19
Fax: 0033.5.56.56.17.15
Email: cedric.galera@u-bordeaux.fr

Table count: 3
Figure count: 2
Words: 3285

Abstract

Backgrounds Cannabis use in ~~postgraduate~~ university students is associated with academic achievement failure and health issues. The objective of the study was to evaluate the association between ADHD symptoms and cannabis use after one year among students according to previous cannabis use.
Methods: Students in France were recruited from February 2013 to July 2020 in the I-Share cohort. 4270 participants were included (2135 who never used cannabis at inclusion and 2135 who did). The Adult ADHD Self-Report Scale (ASRS) was used to assess ADHD symptoms at inclusion. Cannabis use frequency was evaluated one year after inclusion. Multinomial regressions were conducted to assess the association between inclusion ADHD symptoms and cannabis use after one year.
Results Increase in ASRS scores was linked with a greater probability to use cannabis after one year and to have a higher cannabis use frequency (Once a year - Once a month adjusted OR: 1.24 (1.15 - 1.34), More than once a month adjusted OR: 1.43 (1.27 - 1.61)). Among participants who never used cannabis at inclusion, this association disappeared (Once a year - Once a month adjusted OR: 1.15 (0.95 - 1.39), More than once a month adjusted OR: 1.16 (0.67 - 2)) but remained in participants who ever used cannabis at inclusion (Once a year - Once a month adjusted OR: 1.17 (1.06 - 1.29), More than once a month adjusted OR: 1.35 (1.18 – 1.55)).
Conclusions: High levels of ADHD symptoms in students could lead to continued cannabis use rather than new initiations.

Words: 249

Key words

ADHD; cannabis; students; epidemiology; cohort study

Introduction

Cannabis use during ~~postgraduate studies~~ postgraduation from secondary school studies has been associated with a range of adverse outcomes. Notably, current cannabis use ~~leads to~~ is associated with a greater risk of sexually transmitted infections through higher risk-taking behaviors (1). ~~It~~ Cannabis use frequency has also been linked to reduced class attendance, lower academic performance, and less completion of a graduate degree (2–4). ~~Young adult cannabis use in is related to social welfare assistance and unemployment later in life~~ In a Swedish study, heavy cannabis use at 18 years was associated significantly with social welfare assistance (relative risk = 1.38, 95% confident interval = 1.19–1.62) and unemployment (relative risk = 1.26, 95% confident interval = 1.04–1.53) at the age of 40 (5). In young adults, the risk of depression could be increased by cannabis use (6), and some individuals are exposed to a higher risk of schizophrenia (7) with potential involvement of the catechol-O-methyltransferase (COMT) gene polymorphisms (8).

Risk factors for daily cannabis use in young adults are being male, personal and family stress, impulsivity, low self-esteem, and tobacco smoking (9). Among risk factors for cannabis use at the individual level, attention deficit hyperactivity disorder (ADHD) could play a specific role. This neuro-developmental disorder, which is characterized by ~~attention-deficit, hyperactivity, and impulsivity~~ inattention, hyperfocus, hyperactivity, impulsivity, emotional dysregulation, and excessive mind wandering (10), concerns around 7.2% of children and adolescents and 2% of adults (11,12). ADHD is a known risk factor for substance use (13–17) and substance use disorder (18–22). An association between ADHD and cannabis use has been suggested by previous studies (13,15,16,18,23). In their meta-analysis, Lee et al. (2011) reported an increased odd of lifetime cannabis use for people with ADHD in childhood (OR = 2.78, 95% CI = 1.64-4.74) (19). The meta-analysis of Charach et al. (2011) found that ADHD diagnosed in childhood significantly increased the risk of cannabis use disorder during young adulthood (OR = 1.51, 95% CI = 1.02-2.24) (20). Of note, genetic overlap between ADHD and cannabis use and a causal relationship has been reported (24–26). Using large meta-analysis of genome-wide association studies, Artigas et al. (2019) showed a genetic significant correlation (R2 = 0.29, p = 1.63 x 10-5) between ADHD and lifetime cannabis use. In addition, using a two-sample Mendelian randomization approach, Artigas et al. (2019) found arguments supporting that ADHD is causal for lifetime cannabis use (OR = 7.9, 95% CI = 3.72,-15.51) (24).

Studies focusing on the association between ADHD and cannabis use have provided controversial results (presence and absence of association) (16,18,27–34). Prior research in the area is somewhat limited. First, there are few studies on young adults, although they represent the most at-risk population regarding cannabis use. Second, most of the available data for young adults rely on cross-sectional designs, thereby hindering inferences regarding the temporal pattern of the association between ADHD and cannabis use. Third, despite the relevance of psycho-social factors with respect to cannabis use, previous studies lacked a comprehensive adjustment on such factors. Consequently, a residual confusion may impede a proper interpretation of the results. Fourth, most studies until now used clinical samples, which limits the generalization of the results to wider non-clinical populations. Fifth, most of them considered cannabis use and did not explore the influence of use frequency.

~~Our hypothesis is that ADHD symptoms are contributing to increase the use of cannabis at the beginning of adulthood.~~ We hypothesize that ADHD symptoms at the beginning of adulthood contribute to :1) subsequent higher frequency of cannabis use, 2) initiate cannabis use in the students without prior history of cannabis use, 3) maintain the use of cannabis in the students with prior history of cannabis use. A better knowledge of the risk factors of cannabis use could contribute to better

targeted public health interventions. ~~Higher education~~ University students are a population exposed to cannabis use that could particularly benefit from specific preventive interventions.

The aim of the study was to assess the ~~effects of~~ association between of ADHD symptoms ~~on~~ and subsequent cannabis use in a large longitudinal cohort of French students, adjusting on a wide range of sociodemographic, lifestyle, and health confounders, and according to previous cannabis use.

Methods

Study design

i-Share is the acronym for Internet-based Students Health Research Enterprise project (www.i-share.fr), an ongoing observational prospective population-based cohort of students in higher education institutions in France, which started in February 2013. The purposes of i-Share are to explore the health, use of addictive substances, and risk behaviors of students. Students were encouraged to participate through active promotion campaigns (via information stands at registration, university emails, lectures, flyers, social media, newsletters). First, participants filled in a registration form on an online portal and then received an email with their login and password. Second, they had 30 days to validate registration and to complete an online self-administered baseline questionnaire. Between 12 and 24 months after the baseline questionnaire, participants filled in a follow-up self-administered questionnaire online. The participants were not compensated in accordance with French laws.

The i-Share project was approved by the appropriate French national regulatory agencies (Commission nationale de l'informatique et des libertés, CNIL, registration number [DR-2013-019]). The i-Share protocol was submitted to the institutional ethics review board (Comité de protection des personnes, Sud-Ouest et Outre Mer III, CPP). All participants gave their written informed consent to the purpose and the course of the study.

Population

Inclusion criteria in i-Share were to understand written French, to be 18 years old or above, and to be currently enrolled in a higher education program at inclusion. For this specific study, we used data available up to July 2020. Only students aged between 18 and 30 years old who completed follow-up after one year were considered for this work.

ADHD symptoms

At inclusion, participants completed the Adult ADHD Self-Report Scale French version 1.1 (ASRS) (35,36). The ASRS is an exploratory tool for ADHD based on the Diagnostic and Statistical Manual of Mental Disorders – IVth edition (DSM-IV) criteria. It is a short and rapidly completed self-report questionnaire. We calculated the global score by adding the 6 items, and we dichotomized the ASRS raw score in "low" and "high" levels using the higher strata (score > 18) as defined in the validation study (37). Both the internal and external validity and the reliability of the ASRS have been demonstrated (35–41).

Cannabis use

At inclusion, participants were asked: "In your lifetime, have you ever used cannabis? -yes ; -no -do not wish to reply". If they answered "do not wish to reply", their answer was treated as missing data.

After one year, participants were asked: "Concerning your use of substances over the last 12 months: did you use cannabis?". If they answered "no", they were included in the "no" category. If they answered "do not wish to reply", their answer was treated as missing data. If they answered "yes", they were asked for frequency of cannabis use by declarative responses among: "every day", "several

times a week", "once a week", "several times a month", "once a month or less", "only once". To obtain a sufficient number of subjects per category, we gathered responses in three new categories: "no", "<= once/month", "> once/month".

Covariates

Covariates were chosen based on previous studies (13–16,42–47,48) and on univariate statistical significant associations between ADHD symptoms at baseline and cannabis use 1 year later. ~~on potential associations with both ADHD symptoms and cannabis use. At inclusion, using the self-administered online questionnaire, we collected: (1) demographic characteristics: age (continuous), sex (male/female); (2) student-related variables: academic level (first three years/fourth year or higher education), pre-college education degree type (literature, economics, scientific/technical), social-support allowance (yes/no), job activity (yes/no); (3) family-related variables: number of siblings (continuous), highest parents' educational level (graduate or undergraduate studies/postgraduate studies), parental separation (yes/no), parental support during childhood (sparsely/a lot), parent with present or past alcohol issue (no/yes), parent with present or past, depression or anxiety, issue (no/yes); (4) psychoactive substance uses: current tobacco smoking (yes/no), alcohol use (less than one a week/once a week or more); (5) comorbidities: suicidal attempt history (yes/no), depression history (yes/no), obsessive-compulsive disorder history (yes/no), anxious disorder history (yes/no), eating disorder history (yes/no), reading disorder history (yes/no), disability history (yes/no); and (6) psychiatric symptoms levels: the short version of the Perceived Stress Scale (PSS; continuous) for stress (49,50).~~ At inclusion, using the self-administered online questionnaire, we collected: (1) demographic characteristics: age (continuous, years), sex (male/female); (2) student-related variables: academic level (first three years/fourth year or more of study after the secondary school graduation, in the higher education programs), education degree type for the final year of secondary school (literature, economics, scientific/technical), social-support allowance (yes/no, having the benefice of financial support by social institutions for the students coming from socially and financially precarious families), job activity (yes/no); (3) family-related variables: number of siblings (continuous), highest parents' educational level (graduate or undergraduate of the secondary school studies/postgraduate of the secondary school studies), parental separation (yes/no), parental support during childhood (sparsely/a lot), parent with present or past alcohol issue (no/yes), parent with present or past, depression or anxiety, issue (no/yes); (4) psychoactive substance uses: current tobacco smoking (yes/no), current alcohol use (less than one a week/once a week or more); (5) comorbidities: suicidal attempt history (yes/no), depression history (yes/no), obsessive-compulsive disorder history (yes/no), anxious disorder history (yes/no), eating disorder history (yes/no), reading disorder history (yes/no), disability history (yes/no); and (6) psychiatric symptoms levels: the short version of the Perceived Stress Scale (PSS; continuous) for stress (49,50).

Statistical Methods

For variables presenting missing data we conducted multiple imputation analyses with the MICE algorithm (51–53) on 50 datasets and 50 iterations. Imputation details, comparisons between available data, complete cases, and imputed data are presented in supplementary material.

First, we described the sociodemographic, lifestyle, and health characteristics, including academic level, psychiatric symptoms, and substance use, in the full sample of participants and according to the history of cannabis use at inclusion. We looked for associations between the cannabis use frequency after one year and the other variables using an analysis of variance or the Kruskal-Wallis rank sum test for continuous variables and the Pearson Chi-squared test with Monte Carlo simulated p-value based

on 10000 replications for discrete variables. We used a violinchart (54) to illustrate the co-evolution of cannabis use after one year and ADHD symptoms according to the history of cannabis use at inclusion.

Second, we conducted multinomial regression model analyses to assess whether baseline ADHD symptoms were linked with cannabis use after one year for the full sample and stratified on the history of cannabis use at inclusion. The stratification of analyses on cannabis use history at baseline allowed us to study the initiation (in the students without prior history of cannabis use) and the continuation of cannabis use (in the students with prior history of cannabis use) at the beginning of adulthood. We used imputed data and we have standardized all continuous variables. Variables were introduced sequentially in the model. We first entered standardized ASRS score as predictor only. Next, we added sex and standardized age. Then, we considered all variables associated with cannabis use. We checked collinearity and we selected variables in a data-based approach via the multinomial least absolute shrinkage and selection operator (LASSO) regression (55). We grouped variables in the lasso regression to keep or to drop a predictor simultaneously in each cumulative link model (56). Ten-fold cross-validation was used to determine the minimal lambda tuning parameter. Lasso regression suggested dropping suicidal attempt history.

Third, we ran sensitivity analyses to test the robustness of the findings: (1) using dichotomized ASRS score as predictor instead of standardized ASRS score; (2) conducting multinomial regressions on complete cases; (3) conducting weighted multinomial regressions. Weights were computed with calibration on margins with a raking method (57,58) based on reference prevalence of sex and academic level from the 2017 national survey on living conditions of students (59).

Alpha risks were fixed at 5 %. All p-values were two-tailed. We used odds ratios (OR) and their 95% confidence intervals (CI) to test the independent associations between levels of cannabis use and ADHD symptoms. We used a likelihood ratio test to explore the global association between ADHD symptoms and cannabis use. We performed all analyses using R version 4.0.5 (60).

Results

Sample description at baseline

A total of 4270 participants met the inclusion criteria and completed the follow-up questionnaire. Among these participants, 2135 never used cannabis at inclusion, and 2135 ever used cannabis at inclusion. The study flowchart is presented in Figure 1.

Insert Figure 1 about here

Among participants, there were 79.7% of women (n = 3405), and the mean age was of 20.2 years (sd = 2.2, range of [18-29]).

Insert Table 1 about here

Regarding cannabis use one year after inclusion for the full sample, 3018 (70.7%) participants had not used it in the year, 944 (22.1%) participants had used cannabis at least once but less than twice a month, 308 (7.2%) participants had used cannabis more than once a month. The mean level of ADHD symptoms at inclusion was of 10.7(sd = 4). Further details are provided in supplementary material.

The global difference across levels of cannabis use frequency after one year for inclusion ASRS raw score was significant for the full sample, for participants who ever used cannabis at inclusion but not for participants who never used cannabis at inclusion (p: < 0.001, p: < 0.001, and p: 0.16). Figure 2

shows the violin chart (54) figuring the relation between ADHD symptoms at inclusion and cannabis use frequency after one year for participants who used and who did not use cannabis at inclusion.

Insert Figure 2 about here

Multinomial regressions

Table 2 shows the association between ADHD symptoms at inclusion and cannabis use frequency after one year. There was an association between ADHD symptoms at inclusion and cannabis use frequency after one year in the total sample (p: < 0.001) with a greater probability to use cannabis between once a year and once a month (adjusted OR: 1.24 (1.15 - 1.34)) and to use cannabis more than once a month (adjusted OR: 1.43 (1.27 - 1.61)). Participants who ever used cannabis at inclusion and with high scores of ADHD symptoms on the ASRS were significantly more likely to use cannabis at least once a year but less than twice a month (adjusted OR: 1.24 (1.15 - 1.34)), and to use cannabis more than once a month (adjusted OR: 1.35 (1.18 - 1.55)) compared to those who did not use cannabis at all. In participants who never used cannabis at inclusion, high scores of ADHD symptoms on the ASRS were not significantly linked to use cannabis at least once a year but less than twice a month (adjusted OR: 1.15 (0.95 - 1.39)), and to use cannabis more than once a month (adjusted OR: 1.16 (0.67 - 2)) compared to those who did not use cannabis at all.

Insert Table 2 about here

Sensitivity analysis

Sensitivity analyses showed the same pattern of results. The associations between standardized ASRS scores and cannabis use frequency remained similar and significant, as shown in Table 3 after (1) using dichotomized ASRS, (2) selecting uniquely complete cases, and (3) weighting on the French student population (respectively for cannabis use less than twice a month: adjusted OR 1.42 (1.01 - 1.99), adjusted OR: 1.27 (1.15 - 1.39), adjusted OR: 1.21 (1.12 - 1.3) ; and for cannabis use more than once a month: adjusted OR 1.86 (1.17 - 2.97), adjusted OR: 1.44 (1.24 - 1.68), adjusted OR: 1.38 (1.22 - 1.55)).

Insert Table 3 about here.

Discussion

Main findings of study

ADHD symptoms were associated with a higher frequency of cannabis use one year later in a population of French students with prior cannabis consumption but not in students with no prior cannabis consumption. This result suggests that ADHD is a potential risk factor for cannabis use continuation but not for initiation during the young-adulthood. Initiation of cannabis use linked to ADHD should have to be done earlier in life. This result ~~extend sprior researchs~~ extends prior results showing that ADHD is a potential risk factor for cannabis use (13,15,16,18).

Comparison with other studies and interpretation

Our results complement prior results on the association between cannabis use disorder and use and inattentive and impulsive/hyperactive symptoms. This association is conflicting when considering ADHD symptoms in childhood and cannabis use in adulthood due to the complex role of oppositional behaviors (18,29–34). Some authors have already reported this association between ADHD symptoms in adolescence and cannabis use in adulthood (34) but not with the focus on no prior cannabis user.

Several hypotheses may explain the prospective link between ADHD and cannabis use. From a genetic perspective, ADHD and substance/cannabis use share a background of common genetic variants

(24,61,62). There are arguments that ADHD is causal for lifetime cannabis use (24). From a neurobiological perspective, treatment by stimulants reduces the use of substance abuse in persons with ADHD (63,64), consistent with the self-medication hypothesis (65). Indeed, some studies report results suggesting that the use of cannabis could reduce ADHD symptoms (66–70). In addition, in students with ADHD, cannabis use is a moderator of ADHD symptoms severity – executive dysfunction relationship and is linked with a reduction of their perceived medications' side effects (66). From a cognitive perspective, a deficit in executive functions such as planning and response inhibition is particularly linked with ADHD (71). Thus, impulsivity and defects in executive functions may play a role in the physio-psycho-pathology of addiction (14). From a social environmental perspective, we found a link between cannabis use and parental separation, a parent having a past or present alcohol issue, and a lack of parental support during childhood. The ADHD - cannabis use association could be the result of multiple additive and synergistic factors at different levels.

Strengths and limitations

This work has methodological strengths including the population studied, the large sample size, the longitudinal design, and the analysis of the use frequency. Our samples included young adult students with a large proportion of women. Young adults are a population particularly at risk for the short- and long-term consequences of cannabis use, and longitudinal data on this issue are sparse. Most of the longitudinal studies have focused on childhood or adolescence. The use frequency relationship between cannabis use and ADHD is particularly important and has been used to examine the link between cannabis use and psychotic symptoms (72).

The study also has some limitations. First, since we analyzed only those who completed the follow-up questionnaire, a large number of participants were removed, thus creating a selection bias. However, weighting for demographic characteristics in our sensitivity analysis did not show any differences in results. Second, we selected French students so our findings may not generalize to other nationalities in view of cultural, legal, and genetic variability. Third, we did not adjust for externalizing disorders (conduct disorder or oppositional defiant disorder) since these variables were not measured in the study. It will be interesting in future studies to take into account externalizing disorders since they have been shown to be predictive of cannabis use disorder ~~Externalizing disorders have been shown to be predictive of cannabis use disorder and could have confounding effects with contradictory results~~ (16,18,21,32,73). ~~Fourth, regarding the direction of the association between ADHD symptoms and cannabis use, cannabis use could lead to ADHD symptoms. However, we used a longitudinal design to avoid this confusion.~~ Fourth, our results could not be generalized to the full population of young adults since the sample consisted in students uniquely. Students could be different from young adults who did not engage in university education after secondary school graduation. Fifth, it must be acknowledged that in the subsample with prior history of cannabis use it is still possible that ADHD symptoms at baseline could be the result of cannabis use.

Implications, unanswered questions and future research

Better knowledge of the risk factors of cannabis use could inform public health interventions specifically targeting these risk factors. Students are a population exposed to cannabis, which could be a specific target for such preventive interventions. For instance, a simple screening tool like the ASRS could be made available during online university registration to help students to test themselves and to receive advice. Furthermore, clinicians could advise their patients with ADHD about the specific risk of cannabis use. This advice should be given during adolescence and young adulthood and could form part of a therapeutic patient education program (74). Randomized controlled trials are needed to

determine which interventions can reduce the risk of cannabis use in persons with ADHD. Of course, some questions remain unanswered. The pathway from ADHD symptoms to cannabis use disorder through high cannabis use frequency could be explored via a mediation analysis Cannabis use could have a self-medication purpose to reduce ADHD symptoms and enhance executive functions (66–70), which is relevant regarding the fact that ~~.~~ ADHD is linked with poorer academic achievement (4,75). Is there a subgroup of ADHD persons using cannabis as self-medication and achieving better academic performance than ADHD persons not using cannabis? Should cannabis be considered for therapeutic use in ADHD persons? ~~Answers to that question could open new perspectives in the understanding of the association between other substances and ADHD.~~

Conclusions

There is an association between ADHD symptoms and cannabis use in young adulthood. ADHD symptoms are not linked to the initiation of cannabis use in students. High levels of ADHD symptoms represent a potential risk factor for both continuation and an increase in cannabis use in students. Since cannabis use has a negative impact in the short, medium, and long term, ADHD symptoms should be targeted early on.

Acknowledgments

We thank the participants for their commitment to this project. The authors are grateful to the i-Share staff for their assistance in data collection and the administration of the project.

Financial Support

The preparation and initiation of the i-Share project was funded by the program 'Invest for future' (reference ANR-10-COHO-05). The i-Share Project is currently supported by an unrestricted grant from the Nouvelle-Aquitaine Regional Council (Conseil Régional Nouvelle-Aquitaine) (grant N° 4370420) and by the Bordeaux 'Initiatives d'excellence' (IdEx) program of the University of Bordeaux (ANR-10-IDEX-03-02). It has also received grants from the Nouvelle-Aquitaine Regional Health Agency (Agence Régionale de Santé Nouvelle-Aquitaine, grant N°6066R-8 R-8), Public Health France (Santé Publique France, grant N°19DPPP023-0), the National Cancer Institute (Insitut national du cancer, grant N°INCa_11502), and the Medical Research Foundation (Fondation pour la recherche).

Conflicts of Interests

J.A.R.Q was on the speakers' bureau and/or acted as consultant for Eli-Lilly, Janssen-Cilag, Novartis, Shire, Takeda, Bial, Shionogui, Lundbeck, Almirall, Braingaze, Sincrolab, Medice and Rubió in the last 5 years. He also received travel awards (air tickets + hotel) for taking part in psychiatric meetings from Janssen-Cilag, Rubió, Shire, Takeda, Shionogui, Bial, Medice and Eli- Lilly. The Department of Psychiatry chaired by him received unrestricted educational and research support from the following companies in the last 5 years: Eli-Lilly, Lundbeck, Janssen- Cilag, Actelion, Shire, Ferrer, Oryzon, Roche, Psious, and Rubió.

M.A reports (5 paste years) outside the submitted work grants from French Health Ministry Research Grant (PHRC), French Addiction Agency Research Grant (MILDT/MILDECA), Aquitaine Regional Council Research Support (CRA); grants from Indivior, personal fees from Bouchara Recordati, Camurus, Indivior, Pfizer.

Authorship Contributors

CT is the scientific coordinator of the iShare project. CT, IM and JA were involved in data collection. FAMJ, CG, OC were involved in data analysis. FAMJ and CG interpreted the data. FAMJ and CG wrote the first draft of the manuscript, and all authors contributed substantially to its revision. All authors have approved and contributed to the final manuscript.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author, F.A.M.J. Restrictions apply to the availability of these data, which were under the French law on protection and regulation of data. However, data are available with the permission of the I-share team through a special request.

Figure 1: Flowchart of Participants

Flowchart shows subjects who never used cannabis at inclusion and who did not complete the follow-up questionnaire. Note vast difference in size between imputed data and complete cases data.

Figure 2: Distribution of ASRS score with mean, and 95% confidence interval of mean among cannabis use levels for nonusers and users of cannabis at baseline

Violin chart with distribution (displayed twice and attached by base), median, quartiles, mean, and 95 % confidence interval of mean of ASRS through levels of cannabis use. Note increase in ADHD symptoms with increasing cannabis use among participants who never used cannabis at baseline and among participants who used cannabis at baseline.

References

1. Soe NMK, Bird Y, Schwandt M, Moraros J. Substance use preferences and sexually transmitted infections among Canadian post-secondary students. *Patient Preference and Adherence*. [Online] 2018;12: 2575–2582. Available from: doi:gft4tz

2. Allen HK, Lilly F, Beck KH, Vincent KB, Arria AM. Graduate degree completion: Associations with alcohol and marijuana use before and after enrollment. *Addictive Behaviors Reports*. [Online] 2018;9. Available from: doi:gfvm3r

3. Arria AM, Caldeira KM, Bugbee BA, Vincent KB, O'Grady KE. The academic consequences of marijuana use during college. *Psychology of Addictive Behaviors: Journal of the Society of Psychologists in Addictive Behaviors*. [Online] 2015;29(3): 564–575. Available from: doi:f7r6jv

4. Galéra C, Melchior M, Chastang J-F, Bouvard M-P, Fombonne E. Childhood and adolescent hyperactivity-inattention symptoms and academic achievement 8 years later: The GAZEL Youth study. *Psychological Medicine*. [Online] 2009;39(11): 1895–1906. Available from: doi:10.1017/S0033291709005510

5. Danielsson A-K, Falkstedt D, Hemmingsson T, Allebeck P, Agardh E. Cannabis use among Swedish men in adolescence and the risk of adverse life course outcomes: Results from a 20 year-follow-up study. *Addiction (Abingdon, England)*. [Online] 2015;110(11): 1794–1802. Available from: doi:f3phpr

6. Esmaeelzadeh S, Moraros J, Thorpe L, Bird Y. Examining the Association and Directionality between Mental Health Disorders and Substance Use among Adolescents and Young Adults in the U.S. And Canada and Meta-Analysis. *Journal of Clinical Medicine*. [Online] 2018;7(12). Available from: doi:gft84m

7. Manrique-Garcia E, Zammit S, Dalman C, Hemmingsson T, Andreasson S, Allebeck P. Cannabis, schizophrenia and other non-affective psychoses: 35 years of follow-up of a population-based cohort. *Psychological Medicine*. [Online] 2012;42(6): 1321–1328. Available from: doi:czjs7x

8. Costas J, Sanjuán J, Ramos-Ríos R, Paz E, Agra S, Tolosa A, et al. Interaction between COMT haplotypes and cannabis in schizophrenia: A case-only study in two samples from Spain. *Schizophrenia Research*. [Online] 2011;127(1): 22–27. Available from: doi:cvrf6g

9. Dugas EN, Sylvestre M-P, Ewusi-Boisvert E, Chaiton M, Montreuil A, O'Loughlin J. Early Risk Factors for Daily Cannabis Use in Young Adults. *Canadian Journal of Psychiatry. Revue Canadienne De Psychiatrie*. [Online] 2018; 706743718804541. Available from: doi:gft4t2

10. Kooij JJS, Bijlenga D, Salerno L, Jaeschke R, Bitter I, Balázs J, et al. Updated European Consensus Statement on diagnosis and treatment of adult ADHD. *European Psychiatry*. [Online] 2019;56: 14–34. Available from: doi:10.1016/j.eurpsy.2018.11.001

11. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders: DSM-5*. 5th ed. Washington, D.C: American Psychiatric Association; 2013.

12. Thomas R, Sanders S, Doust J, Beller E, Glasziou P. Prevalence of attention-deficit/hyperactivity disorder: A systematic review and meta-analysis. *Pediatrics*. [Online] 2015;135(4): e994–1001. Available from: doi:10.1542/peds.2014-3482

13. Ameringer KJ, Leventhal AM. Associations between attention deficit hyperactivity disorder symptom domains and DSM-IV lifetime substance dependence. *The American Journal on Addictions*. [Online] 2013;22(1): 23–32. Available from: doi:gfj4j4

14. Roberts W, Peters JR, Adams ZW, Lynam DR, Milich R. Identifying the facets of impulsivity that explain the relation between ADHD symptoms and substance use in a nonclinical sample. *Addictive Behaviors*. [Online] 2014;39(8): 1272–1277. Available from: doi:f56cnc

15. De Alwis D, Lynskey MT, Reiersen AM, Agrawal A. Attention-deficithyperactivity disorder subtypes and substance use and use disorders in NESARC. *Addictive Behaviors*. [Online] 2014;39(8): 1278–1285. Available from: doi:f56cvg

16. Elkins IJ, Saunders GRB, Malone SM, Keyes MA, McGue M, Iacono WG. Associations between childhood ADHD, gender, and adolescent alcohol and marijuana involvement: A causally informative design. *Drug and Alcohol Dependence*. [Online] 2018;184: 33–41. Available from: doi:gc73v6

17. Anker E, Haavik J, Heir T. Alcohol and drug use disorders in adult attention-deficit/hyperactivity disorder: Prevalence and associations with attention-deficit/hyperactivity disorder symptom severity and emotional dysregulation. *World Journal of Psychiatry*. [Online] Baishideng Publishing Group Inc.; 2020;10(9): 202–211. Available from: doi:ghjbpx

18. Bidwell LC, Henry EA, Willcutt EG, Kinnear MK, Ito TA. Childhood and current ADHD symptom dimensions are associated with more severe cannabis outcomes in college students. *Drug and Alcohol Dependence*. [Online] 2014;135: 88–94. Available from: doi:gdsj94

19. Lee SS, Humphreys KL, Flory K, Liu R, Glass K. Prospective association of childhood attention-deficit/hyperactivity disorder (ADHD) and substance use and abuse/dependence: A meta-analytic review. *Clinical Psychology Review*. [Online] 2011;31(3): 328–341. Available from: doi:d494nm

20. Charach A, Yeung E, Climans T, Lillie E. Childhood attention-deficit/hyperactivity disorder and future substance use disorders: Comparative meta-analyses. *Journal of the American Academy of Child and Adolescent Psychiatry*. [Online] 2011;50(1): 9–21. Available from: doi:fgt2vf

21. Vogel T, Dom G, van de Glind G, Studer J, Gmel G, Strik W, et al. Is attention deficit/hyperactivity disorder among men associated with initiation or escalation of substance use at 15-month follow-up? A longitudinal study involving young Swiss men: ADHD and substance use. *Addiction*. [Online] 2016;111(10): 1867–1878. Available from: doi:gfj4hr

22. Groenman AP, Janssen TWP, Oosterlaan J. Childhood Psychiatric Disorders as Risk Factor for Subsequent Substance Abuse: A Meta-Analysis. *Journal of the American Academy of Child and Adolescent Psychiatry*. [Online] 2017;56(7): 556–569. Available from: doi:gbnrg3

23. Petker T, DeJesus J, Lee A, Gillard J, Owens MM, Balodis I, et al. Cannabis use, cognitive performance, and symptoms of attention deficit/hyperactivity disorder in community adults. *Experimental and Clinical Psychopharmacology*. [Online] 2020; Available from: doi:ggr3vc

24. Artigas MS, Sánchez-Mora C, Rovira P, Richarte V, Garcia-Martínez I, Pagerols M, et al. Attention-deficithyperactivity disorder and lifetime cannabis use: Genetic overlap and causality. *Molecular Psychiatry*. [Online] 2019; 1. Available from: doi:gfwhcd

25. Demontis D, Rajagopal VM, Thorgeirsson TE, Als TD, Grove J, Leppälä K, et al. Genome-wide association study implicates CHRNA2 in cannabis use disorder. *Nature Neuroscience*. [Online] 2019;22(7): 1066–1074. Available from: doi:gf362f

26. Wimberley T, Agerbo E, Horsdal HT, Ottosen C, Brikell I, Als TD, et al. Genetic liability to ADHD and substance use disorders in individuals with ADHD. *Addiction (Abingdon, England)*. [Online] 2019; Available from: doi:ggrqmw

27. Bussing R, Mason DM, Bell L, Porter P, Garvan C. Adolescent outcomes of childhood attention-deficit/hyperactivity disorder in a diverse community sample. *Journal of the American Academy of Child and Adolescent Psychiatry*. [Online] 2010;49(6): 595–605. Available from: doi:fqsp9c

28. Farmer RF, Seeley JR, Kosty DB, Gau JM, Duncan SC, Lynskey MT, et al. Internalizing and externalizing psychopathology as predictors of cannabis use disorder onset during adolescence and early adulthood. *Psychology of Addictive Behaviors: Journal of the Society of Psychologists in Addictive Behaviors*. [Online] 2015;29(3): 541–551. Available from: doi:f7r583

29. Galéra C, Bouvard M-P, Melchior M, Chastang J-F, Lagarde E, Michel G, et al. Disruptive symptoms in childhood and adolescence and early initiation of tobacco and cannabis use: The Gazel Youth study. *European Psychiatry: The Journal of the Association of European Psychiatrists*. [Online] 2010;25(7): 402–408. Available from: doi:d9hkfr

30. Galéra C, Bouvard MP, Messiah A, Fombonne E. Hyperactivity-inattention symptoms in childhood and substance use in adolescence: The youth gazel cohort. *Drug and Alcohol Dependence*. [Online] 2008;94(1-3): 30–37. Available from: doi:d8hbfh

31. Galéra C, Pingault J-B, Fombonne E, Michel G, Lagarde E, Bouvard M-P, et al. Attention problems in childhood and adult substance use. *The Journal of Pediatrics*. [Online] 2013;163(6): 1677–1683.e1. Available from: doi:f2nx6v

32. Pingault J-B, Côté SM, Galéra C, Genolini C, Falissard B, Vitaro F, et al. Childhood trajectories of inattention, hyperactivity and oppositional behaviors and prediction of substance abuse/dependence: A 15-year longitudinal population-based study. *Molecular Psychiatry*. [Online] 2013;18(7): 806–812. Available from: doi:gfj4j5

33. Fergusson DM, Lynskey MT, Horwood LJ. Conduct problems and attention deficit behaviour in middle childhood and cannabis use by age 15. *The Australian and New Zealand Journal of Psychiatry*. [Online] 1993;27(4): 673–682. Available from: doi:bjw7ct

34. Zohsel K, Baldus C, Schmidt MH, Esser G, Banaschewski T, Thomasius R, et al. Predicting later problematic cannabis use from psychopathological symptoms during childhood and adolescence: Results of a 25-year longitudinal study. *Drug and Alcohol Dependence*. [Online] 2016;163: 251–255. Available from: doi:f8tgb6

35. Caci H, Bayle FJ, Bouchez J. Adult ADHD: Translation and factor analysis of the ASRS-1.1. *European Psychiatry*. [Online] 2008;23: S367–S368. Available from: doi:b9wzwf

36. Kessler RC, Adler L, Ames M, Demler O, Faraone S, Hiripi E, et al. The World Health Organization Adult ADHD Self-Report Scale (ASRS): A short screening scale for use in the general population. *Psychological Medicine*. 2005;35(2): 245–256.

37. Kessler RC, Adler L, Gruber MJ, Sarawate CA, Spencer T, Van Brunt DL. Validity of the World Health Organization Adult ADHD Self-Report Scale (ASRS) Screener in a representative sample of health plan members. *International journal of methods in psychiatric research*. [Online] 2007;16(2): 52–65. Available from: doi:bxwt3x

512 38. van de Glind G, van den Brink W, Koeter MWJ, Carpentier P-J, van Emmerik-van Oortmerssen
513 K, Kaye S, et al. Validity of the Adult ADHD Self-Report Scale (ASRS) as a screener for adult ADHD in
514 treatment seeking substance use disorder patients. *Drug and Alcohol Dependence*. [Online]
515 2013;132(3): 587–596. Available from: doi:f247jp

516 39. Green JG, DeYoung G, Wogan ME, Wolf EJ, Lane KL, Adler LA. Evidence for the reliability and
517 preliminary validity of the Adult ADHD Self-Report Scale v1.1 (ASRS v1.1) Screener in an adolescent
518 community sample. *International Journal of Methods in Psychiatric Research*. [Online] 2018; e1751.
519 Available from: doi:gfrgdw

520 40. Gray S, Woltering S, Mawjee K, Tannock R. The Adult ADHD Self-Report Scale (ASRS): Utility in
521 college students with attention-deficit/hyperactivity disorder. *PeerJ*. [Online] 2014;2: e324. Available
522 from: doi:gfrgdq

523 41. Kiatrungrit K, Putthisri S, Hongsanguansri S, Wisajan P, Jullagate S. Validity and Reliability of
524 Adult ADHD Self-Report Scale Thai Version (ASRS-V1.1 TH). *Shanghai Archives of Psychiatry*. [Online]
525 2017;29(4): 218–227. Available from: doi:gfrgdx

526 42. Cayouette-Remblière J, Saint-Pol T de. Le sinueux chemin vers le baccalauréat : entre
527 redoublement, réorientation et décrochage scolaire. *Economie et Statistique*. [Online] Persée -
528 Portail des revues scientifiques en SHS; 2013;459(1): 59–88. Available from:
529 doi:10.3406/estat.2013.10011

530 43. Kirby T, Barry AE. Alcohol as a Gateway Drug: A Study of US 12th Graders. *Journal of School*
531 *Health*. [Online] 2012;82(8): 371–379. Available from: doi:gf4gn2

532 44. Maldonado-Molina MM, Lanza ST. A Framework to Examine Gateway Relations in Drug Use:
533 An Application of Latent Transition Analysis. *Journal of Drug Issues*. [Online] SAGE Publications Inc;
534 2010;40(4): 901–924. Available from: doi:f3wfdd

535 45. Spilka S, Le Nézet O, Janssens E, Brissot A, Philippon A, Shah J, et al. Les drogues à 17 ans :
536 Analyse de l'enquête ESCAPAD 2017. *Tendances*. 2018;(123).

537 46. van den Bree MBM, Pickworth WB. Risk Factors Predicting Changes in Marijuana Involvement
538 in Teenagers. *Archives of General Psychiatry*. [Online] 2005;62(3): 311. Available from: doi:bt2h5x

539 47. Wüstner A, Otto C, Schlack R, Hölling H, Klasen F, Ravens-Sieberer U. Risk and protective
540 factors for the development of ADHD symptoms in children and adolescents: Results of the
541 longitudinal BELLA study. *PLoS ONE*. [Online] 2019;14(3). Available from: doi:ghh9c3

542 48. Zapata Roblyer MI, Betancourth S, Grzywacz JG. Risk and Protective Factors for Lifetime
543 Marijuana Use among Colombian Emergent Adults Attending College. *ISSBD bulletin*. 2015;2015(1):
544 5–9.

545 49. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *Journal of health*
546 *and social behavior*. [Online] 1983; 385–396. Available from: doi:d2wgms

547 50. Lesage F-X, Berjot S, Deschamps F. Psychometric properties of the French versions of the
548 Perceived Stress Scale. *International journal of occupational medicine and environmental health*.
549 [Online] 2012;25(2): 178–184. Available from: doi:gfrjnr

550 51. Azur MJ, Stuart EA, Frangakis C, Leaf PJ. Multiple imputation by chained equations: What is it
551 and how does it work?: Multiple imputation by chained equations. *International Journal of Methods*
552 *in Psychiatric Research*. [Online] 2011;20(1): 40–49. Available from: doi:cfbxfz

52. Buuren S van, Groothuis-Oudshoorn K. Mice: Multivariate Imputation by Chained Equations in R. *Journal of Statistical Software*. [Online] 2011;45(1): 1–67. Available from: doi:gbw279

53. van Buuren S, Groothuis-Oudshoorn K. *Mice: Multivariate Imputation by Chained Equations*. 2018.

54. Hintze JL, Nelson RD. Violin plots: A box plot-density trace synergism. *The American Statistician*. 1998;52(2): 181–184.

55. Tibshirani R. Regression shrinkage and selection via the lasso. *Journal of the Royal Statistical Society. Series B (Methodological)*. [Online] 1996; 267–288. Available from: doi:gfn45m

56. Yuan M, Lin Y. Model selection and estimation in regression with grouped variables. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*. [Online] 2006;68(1): 49–67. Available from: doi:fvntrnX

57. Deville J-C, Särndal C-E, Sautory O. Generalized raking procedures in survey sampling. *Journal of the American statistical Association*. [Online] 1993;88(423): 1013–1020. Available from: doi:gd59pv

58. Deville J-C, Särndal C-E. Calibration estimators in survey sampling. *Journal of the American statistical Association*. [Online] 1992;87(418): 376–382. Available from: doi:gdwrx9

59. ONVE O national de la vie étudiante. *Enquête nationale conditions de vie des étudiant-e-s 2016 : Données sociodémographiques et académiques*. 2017.

60. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2020.

61. Carey CE, Agrawal A, Bucholz KK, Hartz SM, Lynskey MT, Nelson EC, et al. Associations between Polygenic Risk for Psychiatric Disorders and Substance Involvement. *Frontiers in Genetics*. [Online] 2016;7. Available from: doi:gfj4gh

62. Sanchez-Roige S, Fontanillas P, Elson SL, Gray JC, de Wit H, MacKillop J, et al. Genome-wide association studies of impulsive personality traits (BIS-11 and UPPSP) and drug experimentation in up to 22,861 adult research participants identify loci in the CACNA1I and CADM2 genes. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*. [Online] 2019; Available from: doi:gfv8d9

63. Biederman J. Pharmacotherapy for attention-deficit/hyperactivity disorder (ADHD) decreases the risk for substance abuse: Findings from a longitudinal follow-up of youths with and without ADHD. *The Journal of Clinical Psychiatry*. 2003;64 Suppl 11: 3–8.

64. Looby A. Childhood attention deficit hyperactivity disorder and the development of substance use disorders: Valid concern or exaggeration? *Addictive Behaviors*. [Online] 2008;33(3): 451–463. Available from: doi:bhcmzb

65. Loflin M, Earleywine M, De Leo J, Hobkirk A. Subtypes of attention deficit-hyperactivity disorder (ADHD) and cannabis use. *Substance Use & Misuse*. [Online] 2014;49(4): 427–434. Available from: doi:gfj4jz

66. Stueber A, Cuttler C. Self-Reported Effects of Cannabis on ADHD Symptoms, ADHD Medication Side Effects, and ADHD-Related Executive Dysfunction. *Journal of Attention Disorders*. [Online] SAGE Publications Inc; 2021; 10870547211050949. Available from: doi:10.1177/10870547211050949

67. Asherson P, Cooper R. Treatment of ADHD with Cannabinoids. *European Psychiatry*. [Online] Cambridge University Press; 2017;41(S1): S55–S55. Available from: doi:10.1016/j.eurpsy.2017.01.031

68. Cooper RE, Williams E, Seegobin S, Tye C, Kuntsi J, Asherson P. Cannabinoids in attention-deficit/hyperactivity disorder: A randomised-controlled trial. *European Neuropsychopharmacology*. [Online] 2017;27(8): 795–808. Available from: doi:gbsmv8

69. Mansell H, Quinn D, Kelly LE, Alcorn J. Cannabis for the Treatment of Attention Deficit Hyperactivity Disorder: A Report of 3 Cases. *Medical Cannabis and Cannabinoids*. [Online] Karger Publishers; 2022;5(1): 1–6. Available from: doi:10.1159/000521370

70. Mitchell JT, Sweitzer MM, Tunno AM, Kollins SH, McClernon FJ. 'I use weed for my ADHD': A qualitative analysis of online forum discussions on cannabis use and ADHD. *PLoS ONE*. [Online] US: Public Library of Science; 2016;11(5). Available from: doi:10.1371/journal.pone.0156614

71. Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF. Validity of the executive function theory of attention-deficit/hyperactivity disorder: A meta-analytic review. *Biological Psychiatry*. [Online] 2005;57(11): 1336–1346. Available from: doi:ffqgtz

72. Le Bec P-Y, Fatséas M, Denis C, Lavie E, Auriacombe M. [Cannabis and psychosis: search of a causal link through a critical and systematic review]. *L'Encephale*. [Online] 2009;35(4): 377–385. Available from: doi:b8d3k7

73. Elkins IJ, McGue M, Iacono WG. Prospective effects of attention-deficit/hyperactivity disorder, conduct disorder, and sex on adolescent substance use and abuse. *Archives of General Psychiatry*. [Online] 2007;64(10): 1145–1152. Available from: doi:brfhnn

74. World Health Organization Regional Office for. Therapeutic patient education : Continuing education programmes for health care providers in the field of prevention of chronic diseases : Report of a WHO working group. 1998;

75. Arnold LE, Hodgkins P, Kahle J, Madhoo M, Kewley G. Long-Term Outcomes of ADHD: Academic Achievement and Performance. *Journal of Attention Disorders*. [Online] SAGE Publications Inc; 2020;24(1): 73–85. Available from: doi:gg29c6