CANNABIS USE AND EDUCATIONAL ATTAINMENT

By

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ABSTRACT

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OBJECTIVE: The objective of this dissertation is to test three hypotheses: 1) there is no association linking a history of any cannabis smoking (including early-onset cannabis use, EOCU) with school entry; 2) there is no association between the entry into primary school and EOCU; and 3) there is no association between EOCU and completing each of the educational milestones beyond primary school: starting but not finishing secondary school, starting tertiary school, and starting but not finishing tertiary school.

METHODS: The estimates for this work are based on cross-sectional national probability sample survey data from 16 countries participating in the World Mental Health Surveys Consortium, 2002-2007. There were 41695 participants, of whom 3113 did not enter into the school trajectory, and 6020 had used cannabis, including 2187 who started using before age 17 (EOCU). The methods included unadjusted and adjusted conditional logistic regression, unconditional logistic regression, and meta-analytic methods for estimation. The sampling plan complexity was taken into account (e.g., using weights based on sample selection probabilities), with Taylor series linearization methods for variance estimation as needed for non-independent observations (e.g., multiple households within sampled neighborhoods).

RESULTS: After adjusting by sociodemographic covariates such as sex and age, there was no association between cannabis use trajectory variables and school entry ($p>0.05$). Based on the

area-matched conditional logistic regression model after statistical adjustment for eighteen meaningful covariates, there was an association between early-onset cannabis smoking and later secondary school failure (meta-analytic odds ratio estimate of 1.9; 95% CI = 1.3, 2.7). This result remained consistent when using the unconditional form of multiple logistic regression and the same set of covariates. Concerning failure to enter post-secondary schooling once secondary schooling has been completed, a departure from the null association was found in area-matched analyses with full covariate terms added to the conditional logistic regression model (meta-analytic odds ratio estimate of 1.4; 95% CI = 1.1, 1.7). However, the unconditional form of multiple logistic regression and the resulting meta-analytic odds ratio of 1.2 did not help to confirm those results (95% CI = 0.8, 1.8). Similar inconsistent results were found in estimating the association between EOCU and completing tertiary school once it started. There was evidence of cross-country variations in the association size for all three educational milestones.

CONCLUSIONS: Cannabis use is rare during the years before one enters primary school. This dissertation's estimates suggest that failure to start school was not predictive of later cannabis smoking. Once schooling starts, there is a consistent finding that those with early-onset cannabis use are more likely not to complete secondary school. There is an association, although somewhat inconsistent, between early-onset cannabis use and failing to achieve the schooling milestones after completing secondary school. In future research, replications will strengthen the evidence and create a more solid evidence base about the underlying mechanisms that link early-onset cannabis smoking with disruption of schooling trajectories. That evidence base may create a foundation for future prevention and control activities at the intersection of public health and public education.

I dedicated this piece of work to Lisset, my beautiful wife. She changed everything and put meaning into my life; her strength and wisdom make me feel sheltered. Maria Gracia, our restless daughter, is as lovely as her-Thanks God!

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KEY TO ABBREVIATIONS

ADHD	Attention deficit hyperactivity disorder
BCS70	British Cohort Study
CAPI	Computer-assisted personal interview
CI	Confidence interval
DAG	Directed acyclic graph
DALYs	Disability-adjusted lived years
DR	Designated respondent
DSE	Depolarization-induced suppression of excitation
DSI	Depolarization-induced suppression of inhibition
DSM	Diagnostic and Statistical Manual of Mental Disorders
EOCU	Early onset cannabis use
EOPDU	Early–onset prescription drugs extramedical use
FCSS	Failing to complete secondary school
FCTS	Failing to completed tertiary school
FEPS	Failing to enter into primary school
FETS	Failing to enter into tertiary school
GABA	Gamma aminobutyric acid
GBD	Global burden of disease
GIR	Gross intake ratio
GRE	Gross enrolment ratio
IDU	Injecting drug use

IQ	Intelligence quotient
IRB	Institutional review board
IRD	Internationally regulated drug
LSD	Lysergic acid diethylamide
LTM	Long-term memory
MDMA	Methylenedioxymethamphetamine
NMDA	N-methyl-D-aspartate
OR	Odds ratio
PAPI	Paper-and-pencil interview
PI	Principal investigator
STM	Short-term memory
THC	Tetrahydrocannabinol
UN	United Nations
UNESCO	United Nations Educational, Scientific and Cultural Organization
UNODC	United Nations Office on Drugs and Crime
USA	United States of America
WHO	World Health Organization
WMH-CIDI	World Mental Health Composite International Diagnostic Interview
WMHS	World Mental Health Survey

CHAPTER 1. AIMS AND OBJECTIVES

Against a background of widespread cannabis smoking in many countries of the world (Degenhardt et al.. 2008), the issue of when young people start smoking cannabis in childhood, early adolescence, and middle adolescence, before neurobiological plasticity falls to adult levels, is of particular concern. A paramount public health concern is about whether early-onset cannabis smoking might threaten successful adaptation for adult social roles, and there is a literature on the possibility that early-onset cannabis smoking might disrupt schooling in several countries of the world (David M. Fergusson and Boden 2008).

This dissertation research project seeks a more global view of the possibility that early-onset cannabis smoking might disrupt successful social adaptation by threatening success to achieve educational milestones, drawing upon epidemiological field survey data from 16 countries that have participated in the World Health Organization World Mental Health Surveys Consortium. For this research, the ages of onset of cannabis smoking have been specified concerning what cannabis smokers say about when they started to use this drug. In some instances, cannabis smoking appears early in childhood (before age 6), but it more often occurs during the years of later childhood and early-mid adolescence (6-16 years) and later (age 17 years and older). After initial analyses based on these three subgroups for the age of onset (before age 6; 6-16 years; >16 years), the research specified an early-onset cannabis use (EOCU) construct, with 'early-onset' defined as cannabis smoking before age 17 years, as in prior World Mental Health Surveys publications on the suspected hazards of EOCU (de Graaf et al. 2010).

Within this context, this dissertation has three aims:

AIM 1: To estimate crude and covariate-adjusted cross-sectional associations that link a history of any cannabis smoking with school entry, as well as to estimate the degree to which entry into primary school might account for or simply predict EOCU, with due attention to background characteristics (sex, age).

AIM 2: To estimate the strength of association between levels of schooling and onset of cannabis before age 17, with due attention to potentially important subgroup variations (e.g., sex, age).

AIM 3: To estimate the association between EOCU and failure to finish each of the educational milestones beyond primary school: starting but not finishing secondary school, starting tertiary school, and starting but not finishing tertiary school.

As is true for most research projects in epidemiology, the results of this dissertation project will not constitute definitive evidence for a causal relationship of any of the detected associations. Among the most severe threats to validity of interpretation in this research, I point out: (a) measurement of cannabis use in a legal environment that continues to mean that juvenile justice and the criminal justice systems could be impeding completeness and accuracy of what young people are willing to report about cannabis, (b) a possible temporal sequencing issue such that the cannabis use post-dates disengagement from schooling, as opposed to cannabis precipitation of school disengagement, and (c) the 'omitted variables' problem, also known as 'model misspecification,' in which unmeasured shared vulnerabilities or related processes might cause a co-occurrence of cannabis use and socially maladaptive outcomes in the educational domain, with no causal association of this particular 'exposure' (EOCU) and this particular outcome (school

expectations not being met). These issues are discussed in more detail in later chapters of this dissertation.

CHAPTER 2. BACKGROUND AND SIGNIFICANCE

2.1. Introductory overview

This section of Chapter 2 provides an overview of the dissertation research project. It builds from the basic introduction and specific aims presented in Chapter 1.

In brief, Chapter 2 describes the background and pertinent prior literature on the topic of cannabis use and educational attainment. Then, the potential public health significance or impact of the research is assessed under the assumption that the research project will be completed successfully. After that, Chapter 3 describes the research approach and the necessary 'materials and methods' of the research project.

Chapter 4 presents the empirical estimates produced in this dissertation research project and is organized with four parts. Part 4.1 presents a description of the study sample, showing characteristics of all persons, with cross-classifications according to the primary 'exposure' variable under study (here, early-onset cannabis smoking), and also the sample distributions according to the suspected hazardous outcome of early-onset cannabis smoking (here, failure to start schooling or to achieve educational milestones once schooling is started). Part 4.2 presents findings based on analyses completed for Aim #1 (i.e., to assess possible associations that link a history of any cannabis smoking, especially that one that starts before age 17, with school entry). Part 4.3 presents findings based on analyses completed for Aim #2 (i.e., to assess a possible association between schooling attainment with early-onset cannabis use). Part 4.4 presents findings

based on analyses completed for Aim #3 (i.e., to assess the association between early-onset cannabis use and failure to complete secondary and tertiary school).

Once these results are presented in Chapter 4, Chapter 5 provides a discussion of the results, starting with a recap of the main findings. Then, selected limitations are reviewed, and directions for future research are sketched.

Chapter 6 is a summary of the significant conclusions from the research project, with a summary of potential implications for future research or public health.

2.2. The epidemiology of cannabis smoking

This brief overview of the epidemiology of cannabis smoking sets the stage for a more detailed introduction to research on the suspected hazards of cannabis smoking, especially suspected hazards in the form of failure to achieve educational milestones. For context, it may be helpful to mention some aspects of the history of cannabis smoking in specific and use of cannabis as a medicinal product in general. In contrast with 20th-century 'designer drugs' such as methylenedioxymethamphetamine (MDMA, 'ecstasy'), the human history of cannabis smoking is not new. Apocryphal evidence from ancient China tells that the use of cannabis was known as early as 2500 or 3000 BC, in the form of a pharmacy book attributed to Emperor Shen Nung. The text indicates the use of cannabis as a medicine for several maladies, such as “female weakness, gout, rheumatism, malaria, beriberi, constipation and absent-mindedness.” In addition to these pharmaceutical properties, the book of Emperor Shen Nung mentions the euphoric properties of the drug, even referring to it as the “Liberator of Sin” (Hart and Ksir 2011). Further, in the Indian

Hemp Commission Report of 1893-94, it is stated that "… Tantric religious works sanction the use, and the custom whatever be its origin may now be said from [times] immemorial…." (Touw 1981) (http://findarticles.com/p/articles/mi_m0ISW/is_247-248/ai_113807045/) (http://www.drugtext.org/Indian-Hemp-Commission-Report/chapter-ix.html, Chapter IX, Paragraph 443, last accessed 14 January 2012).

Another historical reference that speaks of social use in the early centuries of the second millennium (i.e., about 1300 AD), is the story left by Marco Polo about a religious cult called "hashishiya" in the eastern Mediterranean region. Cult members were said to commit homicides, distally motivated by political reasons, but more proximally enabled by cannabis use. The fact that this 'hashishiya' group used cannabis either before or (possibly as a reward) after the assassinations are said to be the origin of the word "hashish" as one of the slang names for resin products of this plant. This apocryphal story also may be the origin of 21st-century concerns about this drug causing violence, as conveyed in government propaganda and the popular mass media (e.g., 'Reefer Madness'), as described by Herer and others (http://www.drugtext.org/library/books/herer.pdf; http://www.druglibrary.org/mags/reefermadness.htm).

These examples from the historical background of human cannabis use establish a context for describing the epidemiology of cannabis smoking, organized in terms of the rubrics suggested by Anthony and Van Etten (1998), included quantity, location, causes, and mechanisms (Anthony, J. C. and Van Etten 1988).

2.2.1. Quantity

Worldwide, for 2013, the United Nations (UN) estimated that between 128 and 232 millions of people aged 15 to 64 years had used cannabis at least once in the last 12 months, which represents about 2.7% to 4.9% of the total global population (United Nations Office on Drugs and Crime 2015). For the year 2019, these numbers went up in a not negligible manner. Thus, the UN reported that the best estimate of the global annual prevalence of cannabis in the population of that age range was between 141 million and 256 million (i.e., from 2.8% to 5.1%)(United Nations Office for Drug Control and Crime Prevention 2021). Numbers like these make cannabis the most commonly used drug among the internationally regulated drugs (IRD) on this planet (National Institute of Drug Abuse 2020), with reports conveying that it accounts for approximately 80% of all types of unauthorized IRD use that occurs worldwide (Wayne Hall and Pacula 2003).

Section 2.2.2 will clarify that cannabis use has global distribution and has a substantial prevalence in many world regions. Nonetheless, the global burden of disease attributed to cannabis remains a challenge to be determined (W. Hall et al. 2006; Wayne Hall and Pacula 2003). This becomes apparent in the 2018 publication by the GBD 2016 Alcohol and Drug Use Collaborators, who reported that the Age-standardised DALYs per 100 000 people for cannabis use disorder was 8.5 (GBD 2016 Alcohol and Drug Use Collaborators, 2018). It can be noted two things from this publication. First, the burden of cannabis is a small fraction of which is attributable to any drug use disorder (including opioid, amphetamine, cannabis, and other drug use disorders) and to alcohol use disorder, for which these estimates are 268.3 and 214.3, respectively. Second, there is no estimation of DALYs considering the contribution of cannabis use to the burden of disease by means other than through cannabis use disorder. Thus, there are unanswered questions about how many Disability-Adjusted Lived Years (DALYs) can be attributable to the use of this psychotropic

drug compound specifically. Difficulties in producing this type of estimate became readily apparent during the completion of this dissertation research project. Degenthardt et al. (2013) and the GBD 2016 Alcohol and Drug Use Collaborators, provided new details on cannabis DALYs and global disease burden (Degenhardt et al. 2013) (GBD 2016 Alcohol and Drug Use Collaborators 2018).

2.2.2. Location

Whereas epidemiology's rubric of 'quantity' serves to convey how many individuals might be affected globally, the rubric of 'location' includes estimates of variation in the occurrence of a condition concerning characteristics or conditions of place, time, and person.

Place

Cannabis use has spread all over the world, but it is not evenly distributed across all regions. Figure 2.1 conveys variation in estimates of the annual prevalence of cannabis use among people 15-64 years old across various regions and countries of the world for 2019. The absolute number of users in the Americas has been estimated between 57.5 and 62 million, which represents an annual prevalence between 8.5% and 9.2%, most of the users being in North America with about 47 million recent users. In Europe, the corresponding estimates run between 28.3 and 31.5 million of recently active cannabis users, representing about 5.2% to 5.8% of the region´s total population aged 15 to 64 years. In Asia, between 0.8% (about 24.3 million) and 3.1% (95.2 million) have used cannabis in the last 12 months. Estimates for Oceania show 3.2 million of cannabis users, but in terms of relative prevalence proportions, these numbers make Oceania the region with the current highest prevalence estimates in the world, i.e., the estimated prevalence of between 11.8% and

12.4% of the total population aged 15-64 years. Finally, Africa has between 28.2 and 64.1 million people with past-year cannabis use. It stands as the world region with the second-highest estimates for the prevalence of cannabis use among individuals in the 15-64 years age range (United Nations Office for Drug Control and Crime Prevention 2021). These estimates represent a noticeable increase regarding those reported ten years ago (United Nations Office for Drug Control and Crime Prevention 2011).

Figure 1 Annual prevalence of cannabis use, 2019 (or latest year available)

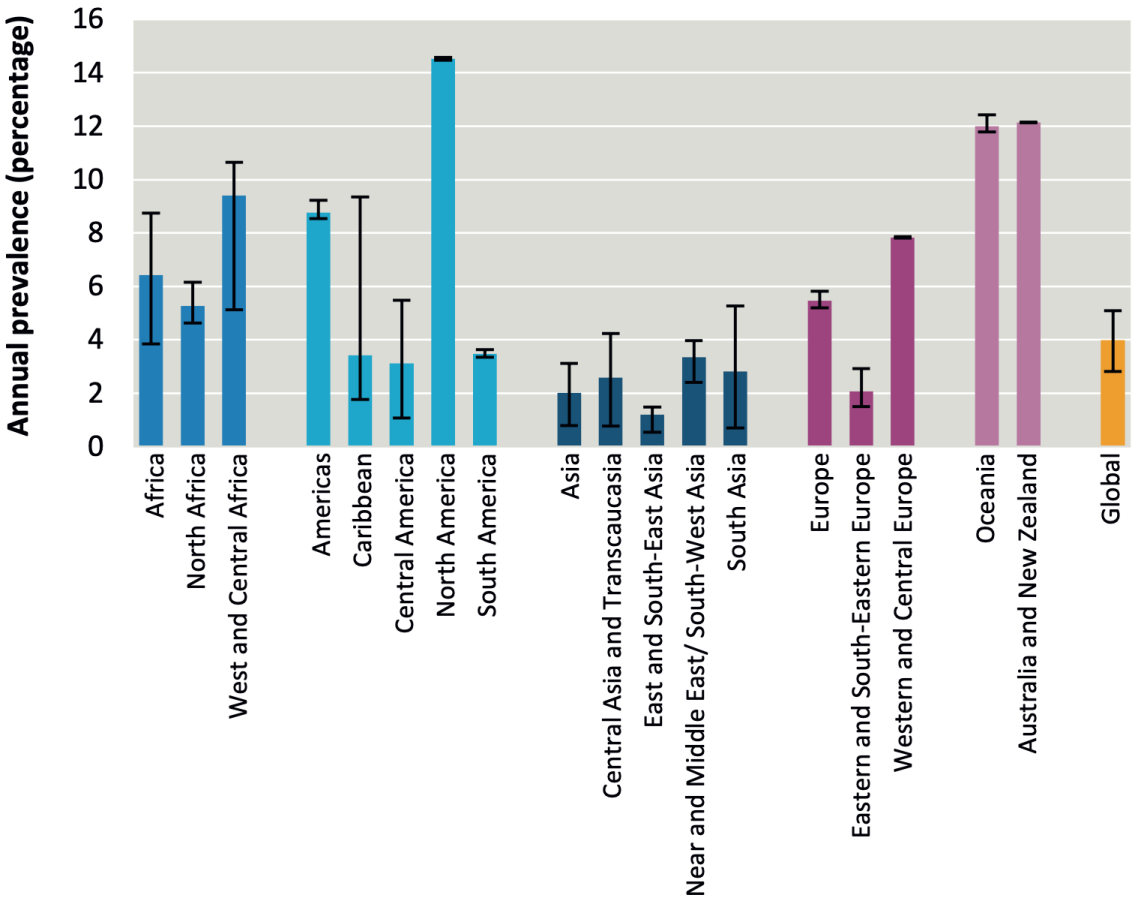


Exhibit from the World Drug Report 2021

Country-level estimates concerning the geographical distribution of cannabis smoking have been reported by Degenhardt et al.. (2008), based upon data from 17 countries participating in the World Mental Health Surveys Initiative. In this study, it was clear that cannabis use prevalence can be very different depending on the countries. In countries such as the United States and New Zealand, cannabis use is widespread in the general population, with cannabis use prevalence estimates of roughly 42% in both countries. These prevalence estimates in the United States and New Zealand are far higher than those seen even in countries traditionally known to have a high prevalence of cannabis use, such as the Netherlands, France, and Germany where the prevalence of cannabis use was found to be 20%, 19% and, 18%, respectively. The rest of the European countries in the World Mental Health Survey (WMHS) showed more variation in the prevalence estimates, with a range in prevalence estimates such as 6.4% for Ukraine and 6.6% for Italy, to 10.4% and 15.9% in Belgium and Spain, respectively (Degenhardt et al. 2008).

Cross-country differences also can be seen within the same region, as illustrated in WMHS estimates for the Middle East and Africa. In two adjacent countries of the eastern Mediterranean, we can see a cannabis prevalence estimate of 4.6% for Lebanon and an estimate of 11.5% for Israel. Wide variation also is seen in Africa, where a relatively low prevalence of cannabis use of 2.7% is seen in Nigeria, while the estimate for South Africa is 8.4%. Asia provides an unusual pattern of variation, with a prevalence estimate of 1.5% seen for Japan, which is five times the prevalence estimate produced for Beijing and Shanghai sites within the People´s Republic of China. In Latin America, a comparison of estimates for Mexico and Colombia showed less variation (8% versus 11%, respectively), but this difference proved to be statistically significant at $p<0.05$ (Degenhardt et al. 2008).

Regarding estimates for the prevalence of recently active cannabis smoking (i.e., in the year before estimation), the 2021 United Nations Office on Drugs and Crime (UNODC) Report shows that there is also a wide variation across countries in the same region. For example, in the Americas, UNODC estimates for recently active cannabis smoking among 15-64-year-olds were 2.1% in México, 2.7% in Colombia, and 19.4% in the United States. Within Europe, the corresponding UNODC estimate for Ukraine is 2.1%, substantially lower than estimates for Belgium, the Netherlands and, France, which have annual prevalences of 7%, 9.6%, and 11%, sequentially. Germany and Spain have intermediate estimated prevalence values of 7.1% and 11%, respectively, while Italy is said to have a substantial prevalence estimate of 10.2% (United Nations Office for Drug Control and Crime Prevention 2021).

In the Middle East and Africa, a wide variation in the estimated prevalence of recently active cannabis smoking among 15-64-year-olds also is evident in some of the UNODC Reports. For example, in Lebanon, the estimated prevalence is only about one-quarter the size of estimates for Israel (e.g., 2% versus 27%). In the case of South Africa, this estimate is roughly 1/3rd the size of the Nigeria estimate (United Nations Office for Drug Control and Crime Prevention 2021).

One suspects that between-country differences in UNODC estimation approaches may account for some of the apparent between-country variations in this region, including a data recollection that occurred at different points in time. Also, it is worth mention that for most of the countries mentioned, the estimates reported in the most recent version of the UNODC (2021) represent an increase in the annual prevalence of cannabis, with exceptions for Germany, Ukraine, and Italy, which experience a slight decrease from the report made in 2011 and 2017. (United Nations Office for Drug Control and Crime Prevention 2011)(United Nations Office for Drug Control and Crime Prevention 2016).

Time

Over-time variation in the occurrence of cannabis smoking appears to be substantial in many regions of the world. For example, cannabis smoking among the European settlers of the United States in the 18th and 19th century appears to have been quite rare; a substantial national epidemic of cannabis smoking emerged only during the Vietnam era in the 20th century, with substantial fluctuations in the occurrence of newly incident cannabis smoking from the 1960s through the early 2000s, e.g., see (James C. Anthony 2006).

These United States time trends are based upon a series of nationally representative sample surveys conducted between the 1970s and the 2000s. Elsewhere, the time trend data are not quite as robust, but the general impression for Canada, Mexico, the European countries, Australia, and New Zealand seems to be a mirroring of the trend pattern seen in the United States, with substantial increases after the middle of the 20th century (UNODC, op. cit.).

A view of time trends, based on critical informant surveys conducted for the United Nations and presented in the World Drug Report 2021, gives a picture of relative stability in recent time trends of cannabis use, at least for about 23% of the 287 reporting experts from the 121 participating countries. However, there appears to be an impression of some temporal variation. For example, a tendency toward increased occurrence and frequency of cannabis smoking seems to hold for most of the experts participating from the UN member countries in Asia, Africa, America, and Europe. Specifically, in Africa and Asia, more than 50% of the local experts reported such an increase in cannabis smoking occurrence and frequency. Within the European region, 32 of 93 experts (34.4%) communicated a sense of increasing cannabis smoking prevalence over time, and 17 of the 55 (30.9%) experts from the Americas gave a similar response. Among the 287 country experts surveyed, the informant impression was one of declining prevalence in only 45

(15.6%) of them (Data from https://www.unodc.org/unodc/en/data-and-analysis/wdr2021_annex.html. Last accessed on July 28, 2021)

Regarding the incidence of cannabis use, evidence also shows fluctuation across time. For example, Gfroerer et al. (2002) estimated that the annual incidence rates in the United States went from a value below 20 per 1000 potential new users aged 12-17 years to a value of more than 60 per 1000 in that specific youthful subpopulation across the range of years from 1965 to 1999. In the subpopulation of young adults aged 18-25, Gfroerer et al. (2002) reported corresponding estimates below 20 newly-incident users per 1000 potential new users in 1965, with an increase to a rate of about 30 newly-incident users per 1000 potential new users in 1999. Working from the Gfroerer et al. (2002), Anthony (2006) produced a United States estimate that in 1999, about 2.5-2.6 million US residents had initiated cannabis in a return to peak values observed in the mid of the 1970´s; the 2017 incidence estimate is roughly the same (James C. Anthony 2006; Gfroerer, Wu, and Penne 2002) (X. Chen et al. 2017) (Lipari et al. 2017).

Person

Concerning the variation in the occurrence of cannabis smoking in relation to characteristics of individuals, the age of onset variable conveys important epidemiological information that can be used to understand the magnitude of psychotropic drug problems, including problems associated with cannabis smoking. Due to compelling evidence that the earlier the involvement (i.e., lower age), the higher likelihood of adverse consequences caused by the drug, although in many instances it is not clear whether earlier age of onset is anything more than a marker of increased cumulative probability of the adverse consequence as might accrue because earlier onset drug users have more time during which drug problems might become manifest (J. C. Anthony and Petronis 1995).

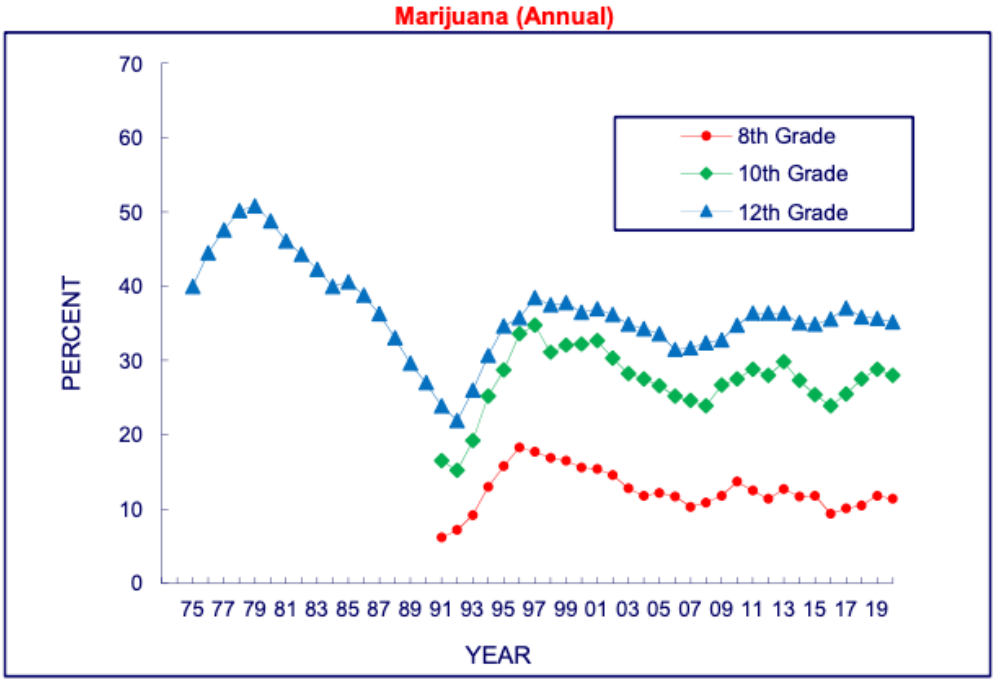
With respect to this aspect of the epidemiology of cannabis use, Degenhardt et al.. (2008), based on data from 17 countries participating in the WMHS initiative found that the median of age of onset of cannabis smoking for most of the participating countries was at 18-19 years, although for some countries cannabis use seems to start some years later. For example, X. Chen et al., discuss mid-adolescent US peak in incidence (X. Chen et al. 2017), whereas in the case of Lebanon, Israel, and Nigeria, an estimated 50% of those who started to use cannabis had done so after age 21/22 years (Degenhardt et al. 2008).

Another view of how populations start using cannabis can be gained by inspecting the estimated percentage of the population with the initiation of drug use by a certain age. Thus, Degenhardt et al. (2008) explored in the WMHS participants who were in the 22-29 years range at the time of the interview the percentage who had started to use cannabis by age 15 years and by age 21 years. The authors found that these percentages mirror the general cumulative incidence of cannabis use, as well as the pattern of differences across countries. For example, based upon the New Zealand and the United States samples, the cumulative occurrence of cannabis smoking by age 15 years was at peak values among the 17 participating countries. Specifically, about 27% and 20% of 22-29-year-olds had tried cannabis by age 15 years in New Zealand (NZ) and in the United States (US), respectively. About 62% in NZ and 62% in the US had done so by age 21 (but see X. Chen et al.., 2017, for survival analysis of approximately 54%). The larger estimates for NZ and US are followed in rank order by estimates from the European countries, then the Middle East countries and Latin American countries, and finally the African and Asian countries. Here again, the pattern mirrors what is seen for the general cumulative incidence of cannabis for each of the countries (Degenhardt et al. 2008).

Variations in the occurrence of cannabis smoking sometimes can be observed across birth cohorts, and the work of Degenhardt and colleagues (2008) included assessment of variation across birth cohort subgroups of the study populations. The authors found that there are indeed variations in cannabis smoking across birth cohorts, corresponding with the time trends discussed above. Specifically, WMHS data show evidence that more recent birth cohorts are at higher risk of starting drugs at any given age than those from earlier birth cohorts and that there is a trend for more recent cohorts to be at higher risk of early-onset cannabis use than those in older cohorts, where early-onset cannabis use is defined by cannabis onset before late adolescence. Also, WMHS data shows that more recent cohorts have a more extended at-risk period than the older ones, meaning that for the younger generations, cannabis use can start even in the twenties. This delayed onset seems to have been quite rare for individuals born earlier in the 20th Century, for whom the middle-late adolescent onset of cannabis smoking was more normative (Degenhardt et al. 2008).

Cohort-specific increases in cannabis use also may be apparent during the past decade of experience in the United States. Based on data from a nationally representative sample of about 50,000 students in grades 8, 10 and 12 attending hundreds of public and private high schools in the United States, the Monitoring the Future study team has found that the annual prevalence of cannabis use has been increasing (Miech et al. 2017). As seen in Figure 2, reproduced an MTF online publication, the ´annual prevalence´ of using cannabis in the prior year, among 12th-graders, grew from 1990 through 1996, and then stabilized, with recent values just under 40%. More fluctuation is seen for 8th and 10th graders in this national sample.

Figure 2 Temporal trend of the annual prevalence of cannabis use among high school students in the United States



Reproduced from Monitoring the Future Report 2020, http://www.monitoringthefuture.org/pubs/monographs/mtf-vol1_2020.pdf , last accessed on July 19th, 2021

Other individual-level characteristics of 'person' are associated with cannabis use. Strong independent predictors or correlates of cannabis use found in the WMH study by Degenhardt et al. (2008) were sex, age, relationship status, family income, and employment status. Specifically, males, younger people, those who are not in a current sentimental relationship, have a family income above average, or those who are working or are students are individual-level characteristics that are strongly associated with a higher risk of having become a cannabis smoker (Degenhardt et al. 2008). Newly incident cannabis use is also strongly associated with age (K. Chen and Kandel 1995; Wagner and Anthony 2002) (X. Chen et al. 2017). Also, minorities may be at higher risk of

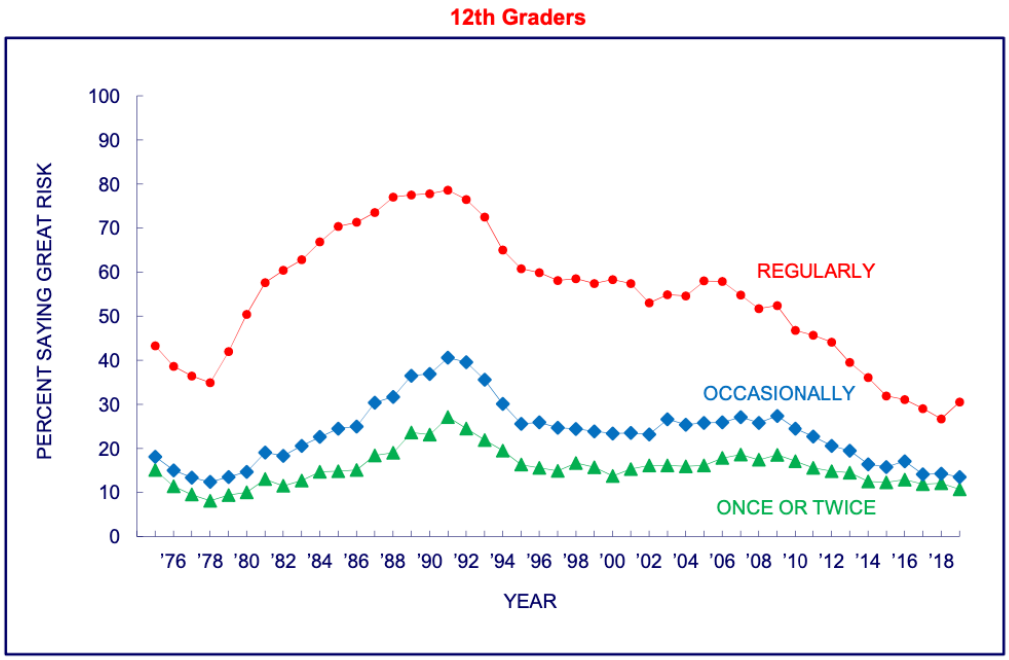
starting cannabis in the US and NZ (James C. Anthony 2006; D. M. Fergusson and Horwood 2000) (X. Chen et al. 2017).

Finally, people living in disadvantageous conditions may be at higher risk of a greater cannabis involvement, once cannabis smoking starts. For example, Pudney (2004) found that individuals living in areas in the lowest 10% distribution of poverty have about 65% more cumulative consumption of cannabis than population members living in other areas (Pudney 2004). Knaappila et al. found consistent findings in a large sample of Finnish adolescents between 14 and 16 years old (n=761,278), drawn of a population-based school survey conducted every two years from 2000 to 2015. Specifically, these authors found that both any and frequent use were associated with indicators of socioeconomic liabilities, such as past-year unemployment of any of the parents (mainly, if it was the case for both parents), low parental education, and not living with both parents. Associations were somewhat stronger for boys and frequent cannabis use versus girls and any use, respectively (Knaappila et al. 2020).

Also, there is controversy about the interaction between person and place. In this regard, some evidence from ecological correlations has found a link between two-time trends: (1) community-level estimates of the degree to which young people regard drug use as harmful, and (2) community-level estimates of the frequency of drug use. Some observers choose to interpret the relationship as causal (Furr-Holden et al. 2011), and others choose to interpret the relationship as an example of ecological fallacy (Parker and Anthony 2018). The first camp draws attention to the plausible connection between a broadly shared public acceptance of the drug and later steps that govern the perceived availability of the drug, whether a young person might be offered a chance to try the drug, and whether the young person might use the drug when it becomes available or is offered. The second camp is more skeptical and wonders whether there might be a

methodological artifact. This artifact has to do with surveys of drug use yielding more accurate and complete self-reports about drug experiences during years following perception of a reduced likelihood of potential incarceration and legal harms directly connected to relaxed police anti-drug activity and less accurate and complete self-reporting during years that follow a perception of an increased likelihood of potential incarceration and legal harms. It is now impossible to judge which of these camps is correct, but in the published epidemiological evidence on cannabis smoking, there is literature documenting sustained increases in the prevalence of recently active cannabis use by high school students that follow or coincide with prior decreases in perceived harmfulness of cannabis smoking. Figure 3 illustrates evidence from ecological correlations of this type, drawn from the United States Monitoring the Future study. Specifically, while the annual prevalence for 12th graders remained relatively constant from 2010 to 2020 (seen in Figure 2), the perception of "great risk" for regular, occasional, and once or twice use continued to go down, more clearly for what it concerns to the use that happens regularly (as seen in Figure 3).

Figure 3 Percentage of people seeing "great risk" in regularly cannabis use



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2.2.3. Causes

As noted above, without the presence of the cannabis product, there can be no cannabis use. As such, cannabis qualifies as a 'necessary' cause of cannabis smoking; in the absence of the cannabis product, cannabis smoking cannot occur. Nonetheless, because the cannabis plant can be grown virtually anywhere on the planet (including the Arctic or Antarctica, where indoor hydroponics can be used) and because non-herbal forms of cannabis-containing products have been marketed in the US and many other parts of the world, it is essential to ask questions about what accounts for some people using cannabis product while others never use it, given presence of the cannabis product in the ambient environment. As outlined in this section, we know very little about the causes of cannabis smoking. To understand why some individuals start using

cannabis while others are spared, it is beneficial to look at the background differences between both groups, the incident cases versus those who are not incident cases up to a certain point in time (e.g., age at interview in epidemiological studies). Given that cannabis is a necessary cause for cannabis use, it can be expected that cannabis availability or exposure opportunity may be one of the most immediate preceding environmental factors that leads to actual use. The literature is compelling in showing that drug availability is a risk factor for drug use, as is seen when it is operationally defined as being associated with peers that use substances (C. Alexander et al. 2001; Coffey et al. 2000; Höfler et al. 1999) or living in a neighborhood with a high proportion of non-users who can be approached to purchase the drug, or with higher incidents of drug possessions (Freisthler et al. 2005; Freisthler, Needell, and Gruenewald 2005).

Nonetheless, there is evidence that suggests that there can be individual-level pre-existing factors, such as genetic factors, that can explain why an individual is in a place with specific characteristics that can make an association with deviant peers or drugs more likely (Gillespie et al. 2007; 2009). This evidence shows that cannabis use is influenced by both environmental and genetic factors (Kendler et al. 2008). Therefore, the environment does not tell the whole story when it comes to explaining why some people use cannabis and others do not. Genetic factors are also involved, and their influence appears to get stronger among older teens and through young adulthood (Gillespie et al. 2007; 2009; Kendler et al. 2008).

In 2017, Anthony et al. published a review about some key epidemiological characteristics that may have a role in causing someone to become a case of cannabis use. In this publication, the authors point out an individual-level aspect that the scientific literature has consistently reported as in relatively constant conjunction with the initiation of cannabis use. Thus, Anthony et al. highlight that the variable socially maladaptive behavior or conduct problem has compelling

supporting evidence as a probable cause of cannabis use incidence, with data coming from both prospective observational and experimental studies. However, as suggested by these authors, the pathways by which the socially maladaptive behavior causes an incident case of cannabis use is still to be determined, especially in the context of other factors that may be contributing to the incidence of cannabis use, although with less supporting evidence of quality. Such variables, with still scarce supporting data regarding their role in the incidence of cannabis use, include parental monitoring and supervision, deviant-peer affiliations, and the availability of the drug in the neighborhood. Other variables in a similar situation of still scarce supporting evidence concerning a potential role in the causal web of cannabis use incidence mentioned by these authors involve those related to the cultural and legal context regarding alcohol, tobacco, and drug use (James C. Anthony, Lopez-Quintero, and Alshaarawy 2017).

2.2.4. Mechanisms

Although the causal chain of events for any given phenomena in nature can be traced back *ad infinitum*, in the study of cannabis use-related health and psychosocial problems it can be advantageous to assume that the starting point is in the first opportunity to use the drug, from which the actual first use of the drug can follow. After the first cannabis trial, some individuals continue using, and some of these develop a maladaptive form of use. Within this subset, some develop abuse or dependence, while others discontinue using or use sporadically with no abuse or dependence syndrome. Other possible outcomes of cannabis use are related to mental and general health; some are psychosocial outcomes such as dampened educational or economic achievements; others involve using other psychotropic drugs.

Evidence shows that the first opportunity to use cannabis is not a random event in the population. Teenagers who are tobacco or alcohol users and those with social and childhood adversities, conduct problems, or with deviant-peer affiliations are more likely to have an opportunity to try cannabis. Also, evidence shows that those who are alcohol and tobacco users are more likely to step into actual use of cannabis given the opportunity to try (Caris et al. 2009; Van Etten and Anthony 1999). And, of these two substances, tobacco use is more intriguing regarding its role in the chain of events that lead to the onset of cannabis use. As Anthony et al. point out, the scientific literature is in general consistent in that the use of tobacco starts before or concurrently with the start of cannabis use. Given these findings, it remains the question if these two life events share common causal determinants or if tobacco use has a causal role in the incidence of cannabis use as suggested by the gateway theory (James C. Anthony, Lopez-Quintero, and Alshaarawy 2017).

There is also evidence that those who use cannabis are more likely to use cocaine and other hard drugs as well as more likely to develop substance abuse or dependence later in life. For example, Lynskey et al. (2003) found in a cross-sectional study performed in monozygotic and dizygotic same-sex twin peers that those who had used cannabis before age 17 were several times more likely to use sedatives (OR=2.8, 95% confidence interval, 95% CI: 1.7, 4.6), hallucinogens (OR=5.2, 95% CI: 2.9, 9.3), cocaine or other stimulants (OR=4.2, 95% CI: 2.6, 6.8) and opioids (OR=2.6, 95% CI: 1.4, 4.8), as well as more likely to abuse or become dependent on other illegal drugs as indicated by OR=2.2 and 95% CI of 1.5, 3.3 (*ibid.*).

The just-cited Lynskey et al. study lends some quantitative support to the so-called "Gateway Theory" which, in the words of Cleveland and Wiebe, implies that "most drug use follows a progressive and structured escalation from tobacco and alcohol to marijuana and then to

´hard´ drugs such as cocaine and heroin" (Cleveland and Wiebe 2008). Some of the arguments pertinent to the plausibility of the gateway hypothesis include the possibility that a) the cannabis-driven neurobiological changes may favor further drug-taking behaviors; b) that the sense of pleasure youths experience with cannabis use may push them to continue the use or to expand the experience toward other drugs; c) that the absence of grave consequences of early drug use may cause the impression in young users that using cannabis is safe and consequently continue using cannabis and even expand it to other illegal drugs; and finally, d) that the contact with the cannabis market implies contact with the market of other illegal drugs, thus increasing the opportunity to try other illegal drugs (M. T. Lynskey et al. 2003).

Nevertheless, scholars have put evidence against the gateway theory. For example, Morral et al., found in a simulation study that the structured escalated progression from cannabis use to the use of other illegal "harder" drugs can be reproduced even in the absence of the assumptions of the gateway theory, favoring instead the alternative explanation that involves a common-factor model (Morral, McCaffrey, and Paddock 2002). There is strong evidence favoring the common-factor model, which supposes that there is a propensity to use drugs, meaning that there is predated liability (possibly genetic) that makes an individual more likely to start using cannabis as well as the use of other illegal drugs. The broader availability of cannabis is the reason why this drug is generally used earlier than the other illegal drugs (Cleveland and Wiebe 2008). However, this issue remains controversial as there is not enough evidence to make a final call regarding which of these competing hypotheses is the most likely or prevalent in real life.

Regarding other aspects of the natural trajectory of cannabis use and its consequences, it can be of advantage to divide possible cannabis effects into those that occur in the short term and those that happen in the long term. In the short term, cannabis has been associated, possibly

causally, with anxiety, panic attacks, and psychosis, as well as disturbances in performance when neuropsychological tests to assess perceptual-motor coordination, information processing, attention, and working memory are administered (Wayne Hall and Degenhardt 2009)(James C. Anthony, Lopez-Quintero, and Alshaarawy 2017). Of particular interest is the report that cannabis use acutely impairs motor behavior, which could explain the over-representation of cannabis users among all types of accidents, including driving accidents (Drummer et al. 2004; Gerberich et al. 2003). Other short-term effects of cannabis use include damage to fetuses and babies, although this evidence remains highly controversial (Wayne Hall and Degenhardt 2009).

Regarding the consequences of using cannabis in the long-term, dependence is perhaps the most studied effect. There is epidemiological evidence that between 2% and 4% of the people who start using cannabis will develop a dependence syndrome within 24 months after that first use of the drug (James C. Anthony 2006; C.-Y. Chen, O'Brien, and Anthony 2005). Going beyond the rate of cannabis dependence that occurs in newly incident cannabis users (i.e., within the 24 months after the first use), with a look at the general proportion of cannabis users that develop dependence regardless of the time they started to use, several research groups estimated that one in 9-11 people who used cannabis at least once in their lifetime develop cannabis dependence, which is more probable to happen within the ten years following first use (Wagner and Anthony 2002; J.C. Anthony, Warner, and Kessler 1994) (Lopez-Quintero et al. 2011)(James C. Anthony, Lopez-Quintero, and Alshaarawy 2017)(National Institute of Drug Abuse 2020).

Other long-term effects of cannabis use described the damage in the respiratory and cardiovascular systems, as well as depression and schizophrenia, although the evidence of these effects remains controversial (Wayne Hall and Degenhardt 2009)(James C. Anthony, Lopez-Quintero, and Alshaarawy 2017)(National Institute of Drug Abuse 2020).

In addition to dependence, cannabis use has been related to several psychosocial outcomes later in life. For example, Ferguson et al., found in a birth cohort in New Zealand followed for 21 years that those with a higher annual frequency of cannabis use had a higher probability of being involved in crime and in the use of drugs other than cannabis, as well as with more probability of depression and suicide ideation (David M. Fergusson, Horwood, and Swain-Campbell 2002). These findings are not surprising given the know neuropsychological effects, both acute and chronic, of cannabis. For example, for someone that is a heavy smoker of cannabis, it is expected that he will spend a significant part of his time using the drug or recovering from its effects on memory, attention, and learning. And there is plenty of evidence that has found that heavy cannabis use is associated with later in life social consequences, like lesser income, unemployment, greater welfare dependence, criminal history, and a generally poorer life satisfaction (National Institute of Drug Abuse 2020). One of the most highlighted associations found in the epidemiology of cannabis use is that it relates to poor educational trajectory (M. Lynskey and Hall 2000). Although several authors entertain the idea that this association is likely to be causal, other authors believe that it is just an association caused by preceding factors that cause both cannabis use and a history of disrupted schooling (Cerdá 2017). More details on this particular relationship are covered in Section 2.3 of this chapter.

2.3. A specific suspected hazard of cannabis use: Failure to achieve educational milestones

2.3.1. Background

Schooling attainment determines future levels of salaries, especially if there is a college education, at least in the United States (Cawley, Heckman, and Vytlacil 2001; J. Heckman, Layne-

Farrar, and Todd 1996). But education also has been found to impact health. This idea, that education might be an important determinant of health, and that health might influence educational attainment, originated as a topic of scholarly investigation in the late 18th century and early 19th century. For example, William Farr, the famous quantitative physician from the 19th Century, assessed the possibility that suicide rates were higher among the more educated places in England using available statistical data. Farr concluded that the higher levels of mortality noted were due to a concurrent increase in the society of "tailors, shoemakers, the small trades, the mechanical occupations," which were jobs involving higher levels of exposures and risk factors (Farr 1841).

More recently, there have been several studies that assess the effect of health, especially health during childhood, on later individuals´ prospects in the labor market and overall personal achievements (Currie 2009). Scientific evidence supports what we can expect intuitively, that child health is directly associated with wellbeing and production later in the individual´s life (J. J. Heckman 2007). This is because poor health early in life tends to have an effect at two levels: a) the child´s schooling performance and other enriching experiences in early life, which in turn affect the acquisition of cognitive and non-cognitive skills needed for successful school attendance and participation in other enriching activities; and b) the parent´s financial opportunities for the child to pursue schooling and other activities, as poor health in a child can drain the already scarce resources that a family has to support those life-enriching experiences. All those missed opportunities caused by lousy health during childhood will end up in less capacity to be competitive for job opportunities and result in further low productivity (J. J. Heckman 2007; M. Marmot et al. 2001; Poulton et al. 2002). Additionally, even events occurring during fetal development can have an impact on mid-term outcomes that can affect schooling and life-enriching experiences in childhood, such as intellectual and social developments (N. Breslau et al.

1994; Brooks-Gunn, Klebanov, and Duncan 1996; Linnet et al. 2006), as well as effects on long-term productivity during adulthood, and outcomes such as employment status (Case, Fertig, and Paxson 2005; Currie and Hyson 1999).

There is also a great deal of evidence showing that education has an independent influence on the well-being of individuals (J. J. Heckman 2012). For example, Richards and Barry (1998) found that males who were 25 years old in 1999 and graduated from college had a life expectancy of 79 years, compared to a life expectancy of 71 years for same-age males who had to drop out from high school (Richards and Barry 1998). This education-related gap in life expectancy has been found to hold over the calendar years (Elo and Preston 1996; Meara, Richards, and Cutler 2008) and across countries (Kunst and Mackenbach 1994; M. G. Marmot, Shipley, and Rose 1984; Mustard et al. 1997).

Besides the relationship found between educational levels and mortality, there is also compelling evidence of the association between educational attainment and other health outcomes and behaviors. For example, recently published research using the British Cohort Study (BCS70), which followed children born in 1970 up to age 30, found that those who attended school beyond the compulsory level were less likely to be obese, suffer from depression or have overall poor health, and less likely to smoke on a daily basis, as well as more likely to exercise more regularly (Conti, Heckman, and Urzua 2010). Similar results were found by Cutler and Lleras-Muney (2010) using a different dataset from the United States and the United Kingdom. These authors found that, after controlling for strong possible confounders, such as age, sex, and parental background, those with higher levels of education were less likely to become smokers, obese, or heavy alcohol drinkers, and more likely to live in safer homes, drive more safely and engage in preventive care (Cutler and Lleras-Muney 2010).

Therefore, education influences future health and achievements of individuals, probably through the promotion of individual cognition, personality, and healthy behaviors, such as exercising, not smoking, better diet, insurance, and safer driving (Conti, Heckman, and Urzua 2010; Conti and Heckman 2010; Cutler and Lleras-Muney 2010).

Concerning levels of education around the world, there has been an increase in the proportion of primary-school-age children enrolled in primary or secondary education. Specifically, this increase has gone from about 85% in 1999 to 90% in 2009, which means an improvement probably due to the extended international mobilization of resources and political commitments to ensure universal primary education in all countries, mainly for those in disadvantaged conditions and poverty (UNESCO Institute for Statistics 2011a). In fact, these improvements are explained by a robust or precise increase in children attending primary school on time in regions such as Sub-Saharan Africa, Arab States, and South and West Asia, while other more affluent regions such as North America, Europe, East Asia, and Pacific, and Latin America continue to have high proportions (mostly about 95%) of primary-school-age children enrolled in primary or secondary education (UNESCO Institute for Statistics 2011a). All these statistics have continued without much variation all through 2018 (UNESCO 2020).

The completion of primary school is better measured using the gross intake ratio (GIR) indicator, which is produced by dividing the number of new entrants to the last grade of primary school in a given year, regardless of the age (numerator), by the population of children in the hypothetical age of entrance to the last grade of primary. In 2011, it was reported that the GIR to the last grade of primary school was 80% or above for about 2/3 of 162 countries, being less for countries in the Sub-Saharan and the Arab States regions (UNESCO Institute for Statistics 2011a). By 2018, this statistic was 90% when taking into account the entire globe. It was lowest for Sub-

Saharan Africa (69%) and highest for Latin America and the Caribbean, Europe, Northern America (between 98%-99%). In the case of Northern Africa, Western Asia, Central and, Southern Asia and Oceania, this estimate was between 87% and 93% (UNESCO 2020).

The transition proportion from primary school to secondary school is also high for most countries. For example, by 2011, for most countries in North America, Europe, and central Asia, this transition proportion is more than 95%, and for Latin America, the Arab States, East Asia, and the Pacific, most countries have a transition proportion in the 90%-100% range. However, in countries in South and West Asia and Sub-Saharan Africa, this educational indicator varies more widely, with most countries standing in the 60%-98% range. By 2018, these numbers reminded pretty similarly (UNESCO 2020).

Although there has been an increase in the attendance of secondary school globally in the last two decades, this increase has not been as sharp as that seen for primary school. As measured by the gross enrolment ratio (GER, the ratio between the total enrolment, regardless of the age, and the targeted population), by 2011, secondary school attendance is higher than 80% for most of the upper-middle- and high-income countries, but between 20-80% in most of the low- and lower-middle-income countries (UNESCO Institute for Statistics 2011b). By 2019, there has been an improvement in these indicators, although the gaps between the poorer and richer countries remain (The World Bank 2021).

Regarding the indicators for completion of secondary school, the gross graduation ratio (i.e., the ratio of the number of graduates of secondary school to the population of graduation age for that level) is more than 60% for most of the countries in North America, Europe, Central and East Asia, and the Pacific, but 60% or less for most countries in Latin America (UNESCO Institute

for Statistics 2011a). For the completion rate indicator, UNESCO reported that by 2018 this statistic for upper secondary was 49% worldwide, being less than 50% for Oceania, Sub-Saharan Africa, and Central and Southern Asia, and 88% for Europa and Northern America. In the case of Northern Africa, Western Asia, Central, and Southern Asia, and Latin America, and the Caribbean, this indicator was between 50% and 60% (UNESCO 2020).

Globally, tertiary school participation has increased dramatically in the last three decades. In 2007, the global average of the gross enrolment ratios was three times the ratio estimated in 1970 (26% versus 9%, respectively). However, there are still substantial differences across regions. For example, in Northern America and Europe, the attendance to tertiary education is much larger than that seen in Latin America and Central Asia (60-70% versus 30-35%, respectively), while countries in the Sub-Saharan region (GER about 6%) and South and West Asia (GER=11%) tend to be more disadvantaged (UNESCO Institute for Statistics 2009). By 2018, GER in tertiary education was 36% worldwide, 77% for Northern America and Europe, 73% for Oceania, and 52% for Latin America and the Caribbean. In Asia, the percentages went from 24% to 56%; and in Africa, from 9% for Sub-Saharan Africa to 35% for Northern Africa (UNESCO 2020).

Regarding the completion of tertiary school, generally, the number of people that graduate from tertiary school mirrors the number of people who attend tertiary school previously shown. Thus, by 2007 most countries in Europe and North America and many in East Asia and the Pacific had a gross graduation ratio above 30%, while in Latin America that measure was between 10% and 25%, and in Sub-Saharan Africa it was less than 10% (UNESCO Institute for Statistics 2009). More recent data about this statistic have been not found by September 2021.

2.3.2. Suspected determinants of educational achievement: A broad range

It is possible to think of a broad range of determinants of educational achievement, some of which qualify as 'macro-social' influences (such as a federal government's investment in educational resources, its promotion of access to education, and laws such as compulsory education and 'school leaving age' regulations). Other determinants operate from the microscopic end of the distribution of ecological scale and include individual-level characteristics such as trisomy-21, which can constrain educational success in school.

Among the individual-level factors, Heckman J (2007) points to lack of ability as the cause of most of the failure in education and poor life outcomes, which includes cognitive skills such as intelligence quotient (IQ), reading comprehension, analytic thinking and problem-solving abilities, and social-emotional skills, which include motivation, self-regulation, and personality. Of these two types of skills, evidence favors the predominant role of the social-emotional skills, as opposed to cognitive ones, as predictors of the individual´s educational achievements and success later in life (J. J. Heckman 2007).

Evidence from studies in economics shows that the educational gap between advantaged and disadvantaged people in society mirrors the gaps in social and cognitive skills, which starts to appear very early in life, even before people start school—although this does not mean that the cognitive and noncognitive skills are genetically determined. In fact, evidence suggests that environmental characteristics or events occurring very early in life have a much more substantial impact in shaping the future and success of people, than those occurring later in life when the child enters into primary school (J. J. Heckman 2013a).

Thus, family and family environments seem to be very influential in creating those social-emotional and cognitive skills important to success in school. For example, Krein and Beller (1988) found that to live in a single-parent family, especially during the early years of schooling, is associated with a lower educational achievement (Krein and Beller 1988).

The role of family environment in the formation of skills in children is better demonstrated by manipulation of what Heckman calls the "the accident of birth," by which it is understood that some children are put in advantaged families while others are put in disadvantaged families. The relation between family and success in school --and in other aspects occurring later in life-- has been evident in several experiments where interventions were randomly assigned to improve conditions of parenting in disadvantaged families. These experiments, placed very early in the life of the participants, improved not only the cognitive abilities but also improved social-emotional skills, which translated into better school achievements and adult outcomes (J. J. Heckman 2013a).

This robust evidence that very early life events determine educational achievements and other aspects in life, such as cannabis smoking, motivates this dissertation´s interest in exploring a possible association between a cannabis use trajectory and education trajectories early in the life of individuals (e.g., entering into primary school and entering into secondary school).

Other characteristics associated with performance in school are related to mental and physical health. For example, Mannuzza et al. (1993) found in a concurrent cohort of young boys followed by intervals ranging from 13 to 19 years that those children diagnosed as hyperactive during childhood (n=91) achieved fewer educational milestones and had lower occupational attainments than those males who did not present hyperactive behaviors but were of similar demographic characteristics, such as race and age (Mannuzza et al. 1993). Subsequently, more

studies have found consistent results linking Attention-deficit/hyperactivity disorder and poorer educational attainment (Loe and Feldman 2007)(Usami 2016).

Similarly, Kessler et al. (1995) showed evidence that early-onset Diagnostic and Statistical Manual of Mental Disorders (DSM)-III-R psychiatric disorders harm educational attainment. Specifically, Kessler et al. found in an epidemiological sample representative of the general population of the United States aged between 15 to 54 years that those who experienced psychiatric disorders (mainly, conduct disorders and substance use disorders for males and anxiety and depression disorders for females) early in life were less likely to complete secondary school and less likely to get into college or complete college among those who entered this level of education (R. C. Kessler et al. 1995).

Consistent with this evidence that mental disorders can impair the probability that an individual will complete higher levels of schooling, Lee et al. (2009), using epidemiological data from 16 countries participating in the WHMS initiative, found that early drug-use and other mental disorders were associated with subsequent failure to complete school milestones (Lee et al. 2009). With similar methodologies using a different dataset, Breslau et al. found consistent results (J. Breslau et al. 2008; 2009). Similarly, Blanco et al. (Blanco et al. 2008) found, in a study with data from the 2001-2002 National Epidemiology Survey on Alcohol and Related Conditions, that college students were less likely than their non-college peers to be diagnosed with a drug use disorder, as well as less likely to have ever used tobacco.

Other factors associated with reduced educational trajectories include sex. For example, Alexander and Eckland found in a longitudinal study of a concurrent cohort that included 2077 high-school students followed for 15 years that there is a net disadvantage for females in the 1950s

to complete more years of schooling, even after controlling for other meaningful covariates, such as ability, background variables, curriculum, type of influence of robust or precise others and college plans (K. L. Alexander and Eckland 1974). More recent estimates present that male-female parity regarding access to education has improved considerably across the globe. Thus, the adjusted gender parity index of gross enrolment ratio by 2018 (or latest available year) for primary education was 1.00, 0.99, and 0.98 for lower and upper secondary, respectively. Interestingly, for tertiary school, this indicator was 1.16 in favor of women. However, this improvement has proved to vary across the world regions, especially for the higher levels of education. For example, the just mentioned indicator was 0.84 and 0.74 for upper secondary and tertiary education, respectively, in Sub-Saharan Africa, while it was 1.00 or higher for both education levels for Europe, Northern America, Latin America, and the Caribbean, and the Eastern and South-eastern Asia (UNESCO 2020).

Hall et al. published in 2016 a comprehensive review concerning substance use as a potential risk factor for lower educational attainment in adolescence and young adulthood. They found evidence of moderate quality (coming from representative population-based cohort studies) that causally linked tobacco, alcohol and cannabis use to poor educational achievement in the before mentioned population group. The evidence is much weaker for the link between the use of other illicit drugs (such as opioids, amphetamines, or cocaine) and that disadvantageous educational outcome (W. D. Hall et al. 2016).

With respect to cannabis use and educational attainment, Fergusson et al. (2003), in a cohort followed from birth up to age 25 performed in New Zealand, found that use of cannabis by age 16 was independently associated with leaving high school without qualifications. The evidence gathered from this study suggested a dose-response association, where a higher frequency of

cannabis use predicts a higher risk of failure to complete high school even after adjusting by a wide range of covariates (David M. Fergusson, Horwood, and Beautrais 2003).

In 2010, Horwood et al. published the results of a study where the age of onset of cannabis was linked to the probability of achieving each of the following educational milestones: completing secondary school, entering and completing tertiary school. The authors used data from three prospective cohorts from Australia (two) and New Zealand (one). They found that, compared with those users who started before age 15, those who started between age 15 and 17, and those who were naïve from cannabis by age 18, were more like to achieve each of the three educational milestones studied. The association between the age of onset and likelihood of completing each of the three educational milestones had a dose-response form (Horwood et al. 2010)(David M. Fergusson, Boden, and Horwood 2015).

Van Ours et al. (2009), using data from the 2001 Australian National Drug Strategy Household Survey (NDSHS), found evidence that cannabis use before age 18 in men and before age 20 in women leads to a reduction of years of education and that this reduction is more extensive in those who started earlier and women. The null hypothesis that educational attainment and age of initiation in cannabis are independent variables was firmly rejected by the Pearson $\chi 2$ test with a p-value <0.001 for both males and females. In males, 43% of non-users failed to complete secondary school, while this estimate was 47% for those who ever used cannabis. In addition, 57% of males who started cannabis use at age 15 fail to complete high school compared to 48% of those who began cannabis use between 16 and 17 years; this pattern is repeated for the other educational categories and between men and women. In males, using cannabis increases the risk of school dropout rate by around 23% compared to non-user peers. In women, this estimate is 51%. The authors also found that initiation of cannabis by age 17 for males, and 19 for women, harm

educational trajectory. Furthermore, the evidence suggested that if a boy starts using cannabis by age 13, the length of their formal education is expected to be shortened by 1.1 years; if consumption begins at age 15, the reduction is about 0.8 years. If a girl starts using marijuana at age 13, the length of her formal education is expected to be reduced by 1.9 years; if consumption begins at age 15, it is shortened by 1.3 years (van Ours and Williams 2009).

Degenhardt et al. (2010) published data from a cohort study conducted in Australia that included 1,943 adolescents aged 14 and followed for ten years, collecting data in eight waves. The authors found that 34% (95% CI: 32, 37) of the participants have used cannabis in the past six months at some point between 14.9 years and 17.4 years; 64% (95% CI 59–68) of them occasionally used, while 36% (95% CI 32–41) used cannabis weekly or daily. Of the adolescents with occasional cannabis use, 71% persisted in the same level of use into their 20s, while 20% escalated to weekly or daily use. In addition, cannabis-using adolescents (both for the occasional user group and weekly or daily user) were less likely to have attained post-school qualifications by age 24 compared to non-users (OR: 0.63, CI 95% CI: 0.47–0.83, for occasional users and OR: 0.41, CI 95%: 0.29–0.58, for weekly or daily user]. However, after adjusting for meaningful covariates, especially tobacco use, all these associations were attenuated to such an extent that they lost statistical significance. The authors interpreted this tobacco-driven attenuation of the effect as an indicator of a possible mediating role of behaviors highly associated with tobacco use, such as deviant peer affiliation. Specifically, the authors found that the adjusted probability of completing high school was less than 30% for those starting cannabis before age 15, 40% for those who started between age 15-17 years, and 50% for those who have not used the drug before age 18. A similar trend applied for the achievement of the other educational milestones, such as university enrolment and university degree attainment (Degenhardt et al. 2010).

Interestingly, although plenty of observational studies has found an association between cannabis use and poor educational trajectory, some twin studies suggest that this association may be due to shared familial factors and not a causal one. For example, Grant et al. (2012), in an elegant twin study performed in veterans in the USA, found that there was no difference in completing at least 16 years of education between the twins who started to use cannabis before age 18 and their discordant twins (adjusted OR: 1.35; 95% CI: 0.76, 2.41). Similar results were found concerning the twin discordancy in the variable of cannabis initiation (OR: 0.9; 95% CI 0.65, 1.24) (Grant et al. 2012).

Leach et al. (2012) performed a study where they analyzed data from the 2007 Australian National Survey of Mental Health and Wellbeing (NSMHWB), which has a stratified, multistage methodology that allows a probabilistic sampling of households from which a member is randomly chosen among the 16 and 85 years to answer the interviews. The sample resulted from 8841 participants, which meant a response rate of 60%. After adjusting for previous traumatic experiences, the authors found that failure to complete the tenth year of education was significantly associated with early-onset (before age 16) cannabis use disorder in males (OR = 8.06, IQ = 1.88–34.63). Not completing the twelfth year (under 18 years) was significantly associated with men's early onset of cannabis use disorder (OR = 3.67, CI = 1.81–7.43). No data are reported for women regarding cannabis use disorder(Leach and Butterworth 2012).

Meier et al. (2015) followed a cohort of 254 teenagers from an upper-middle-class community in the USA, intending to study whether the use of cannabis is associated with poor academic performance while controlling by the potential confounding effect of SES as all the participants were from the same high SES level community. Participants were followed from the age of 14/15 years to 17/18 years. The independent variable is the past-year frequency of cannabis

use, measured annually. The dependent variable was collected from the official school records. The authors found that 19% of the participants had used cannabis each month for approximately two or more years during high school, and 38% never used cannabis. Also, they found that persistent cannabis use throughout four years of high school was associated with a lower 12th grade GPA (β = −0.18; CI 95%: −0.30, −0.05; p = 0.006), even after controlling for 9th grade GPA (β = −0.13; CI 95%: −0.24, −0.03; p = 0.014). The effects were not maintained after controlling for persistent alcohol and tobacco use (β = −0.06; 95% CI: −0.21, 0.09; p = 0.43). Similarly, persistent cannabis use throughout the four years of high school was associated with a lower 12th grade SAT score (β = −0.13, 95% CI: −0.26, −0.007; p = 0.038), although the effect became non-significant after controlling for 9th grade GPA (β = -0.09; 95% CI: - 0.19, 0.01; p = .07). The association between persistent tobacco use and lower SAT scores became non-significant after controlling for persistent cannabis and alcohol use (β = −0.08, 95% CI: - 0.21, 0.05; p = 0.24) . Therefore, this study finds that persistent cannabis use throughout the four years of high school does not have an independent effect on measures of school performance such as GPA and SAT in grade 12th, after taking into account strong confounding covariates (Meier et al. 2015).

For their part, Maggs et al. (2015) carried out another study using data from the Monitoring the Future study in 4925 high-school students to investigate whether the frequency of cannabis use at the age 19-20 years predicts receiving academic degrees by the mid-20s, taking into account the effect of meaningful covariates. The author found that, even though there was an initial statistical association between frequent use of cannabis (that is, more than six occasions in the last 30 days) compared to non-users regarding earning a Bachelor's degree, this was lost after adjusting for substance use at age 18. Similar results arose when comparing frequent users versus infrequent

users (one to six times in the last 30 days). In addition, infrequent users did not differ from non-users of cannabis for any outcomes (Maggs et al. 2015).

Silins et al. (2015) found that those who started to use cannabis before age 17 were more likely to fail to complete secondary school and fail to both enter and complete tertiary school. These authors found this evidence in a study involving three prospective cohorts in Australia and New Zealand. Additionally, the evidence suggested that the associations were not related to the intensity of the cannabis involvement. Specifically, the evidence pointed out that those with less than weekly use among the early-onset cannabis users were at risk as much as those who used it weekly or more (Silins et al. 2015).

Stiby et al. (2015) conducted a birth cohort study in England, where 1155 participants were followed to investigate the association between the use of cannabis or tobacco and the school-related variable at age 16. The analysis considered meaningful covariates related to early in-live events, such as maternal substance use, socioeconomic status, sex, age, educational attainment before age 11 of the participants, child substance use before age 15, and conduct disorder. The authors found that cannabis use by age 15 was associated with all of the disadvantageous educational outcomes studied and that this relationship had a dose-response distribution. However, after considering the potential effect of all the covariates, the effect size was considerably attenuated, although it remained robust for those who had weekly cannabis use compared to non-users. Of particular interest is the association between school dropout and cannabis use by age 15. The study found that ever-used cannabis by age 15 was independently associated with school dropout by age 16 (fully adjusted OR: 2.75; 95% CI: 1.18, 6.39). However, this association was explained by weekly use (fully-adjusted OR: 4.44; 95% CI: 1.79, 11.0) and not by infrequent use (that is, not weekly; fully-adjusted 1.96; 95% CI: 0.74, 5.21). Consistently, a high score on the

cannabis abuse assessment instrument (greater than three on the Cannabis Abuse Screening Test-CAST) was strongly associated with school dropout at age 16 (fully-adjusted OR: 4.40; 95% CI: 1.70, 11.38) (Stiby et al. 2015).

Suerken et al. (2016), in a prospective cohort of 3,146 students from 11 colleges in the USA, found that patterns of cannabis use during college were associated with poor educational trajectories. Specifically, the study evaluated the association between cannabis use trajectories across a seven-semester period during college and academic outcomes by the fall semester of the senior year. To build the cannabis use trajectory variable, the authors used the number of days the person used cannabis in the past 30 days, which was asked in each of the six waves of data collection. The Bayesian analysis of the data resulted in five cannabis use trajectories: non-users (69%), infrequent users (16.6%), decreasing users (4.7%), increasing users (5.8%), frequent users. The educational outcomes included current college enrollment, on-time graduation plan, and grade point average. The authors found that the frequent users and the over-time decreasing users were more likely to drop out and delay graduation from college than non-users. In addition, this study found that all the cannabis user groups were more likely to have lower average GPA than the non-users (Suerken et al. 2016).

Goldschmidt et al. (2016) carried out a rather ambitious study in the USA since it meant following a cohort of 608 individuals from their mothers' pregnancy and up to 22 years. This research collected prenatal variables prospectively at 3, 14, 16, and 22 years of age. In this study, early-onset cannabis use (EOCU) was defined as when cannabis started at age 14 or earlier, lower educational attainment when the individual completed 12 years of schooling or less. This study found that at 22 years of age, those EOCU were less likely to have completed 12 years of education than those who were not EOCU. Unfortunately, the authors did not perform multivariate regression

analysis with this dichotomous variable regarding education but instead performed latent variable analyzes where the outcome was one in which different variables of social achievement were combined with a single latent variable. The social variables that made up the latent variable of adult role maladjustment included, at age 22, working or serving in the military, being arrested, having children while single, and less than 12 years of formal education. The authors found that EOCU was strongly associated with maladjustment to adulthood roles (Goldschmidt et al. 2016).

Melchior et al. (2017) did a study using data from the French TEMPO project where children from 4 to 16 years were assessed in 1991 and then in 1999, and finally in 2009. From the original 1991 sample (n=2582), 1103 children were recontacted (i.e., a response rate of 44.5%). These authors found that, after taking into account meaningful covariates through propensity score-based methods, there was a robust association between early-onset cannabis use (i.e., use by age 16 or earlier) and failing to complete secondary school for females but not for males (Melchior et al. 2017).

Korn et al. (2018) did a prospective study in the USA where they followed a sample of 1915 10th-grade students up to two years after graduating from high school. The authors found that both occasional (less than 20 times during the last 12 months) and frequent use of cannabis (20 times in the previous 12 months) at 10th grade were independently associated with low school achievement (based on grade point average) compared to those who had not used it in the same period, after adjusting by meaningful covariates. Interestingly, the authors found that, compared to non-users, those occasionally cannabis users were more likely to attend university or college two years after completing secondary school, while those frequent users were less likely to participate in tertiary school (Korn et al. 2018).

Nguyen et al. (2020) carried out a study in Canada in which they explored the legal minimum age for the use of cannabis concerning the effects that this use can have on relevant outcomes in the person's life, such as academic achievement. The authors found a direct correlation between the age of onset of marijuana use and the person's level of education. Specifically, those who started cannabis use at 21-24 years had a higher educational level than those who started before 21 ($p < 0.01$). The authors interpreted these results as that the minimum legal age for the use of cannabis not to affect the educational level that the person can achieve is 21 years (Nguyen et al. 2020).

The current dissertation research project, with a focus on cannabis-education relationships, was developed with this background of epidemiological research on cannabis and education in mind. As described below, the project attempts to add new information about relationships between cannabis use and education and to help evaluate whether early-onset cannabis use might cause disruption of educational trajectories or keep young people from achieving educational goals.

CHAPTER 3. MATERIALS AND METHODS

3.1. Background

Chapter 1 presented the specific aims of this dissertation research project concerning early cannabis smoking and educational attainment. Chapter 2 provided an overview of cannabis history and epidemiology, highlighting the adolescent years as an interval of starting cannabis use that might also affect educational achievement during that interval. Chapter 2 also provided an overview of the 19th-century origins and history of epidemiological research on education and health, as well as a literature review on the disruption of educational milestones as a possible hazard of starting to smoke cannabis in childhood or up through mid-adolescence (before age 17 years), with due consideration of other explanations for failure to reach these educational milestones that might function as confounding variables in efforts to estimate cannabis-attributable disruptions.

Figure 4 presents a cartoon for a directed acyclic graph (DAG) that provides a summary overview of the primary relationships to be investigated here, without a depiction of confounding variables. Figure 5 presents an elaboration of the cartoon DAG to depict the possibility of a single confounding variable.

Figure 4 DAG cartoon providing an overview of the primary relationships

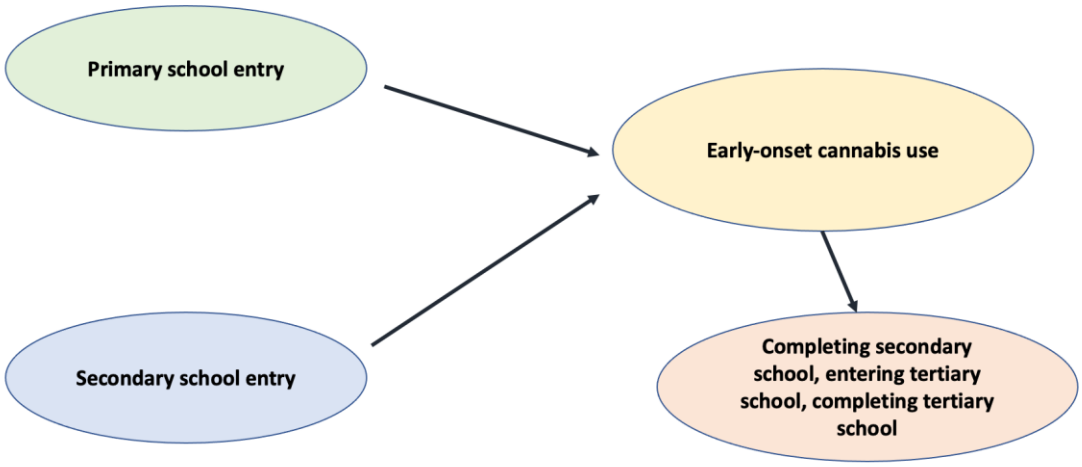
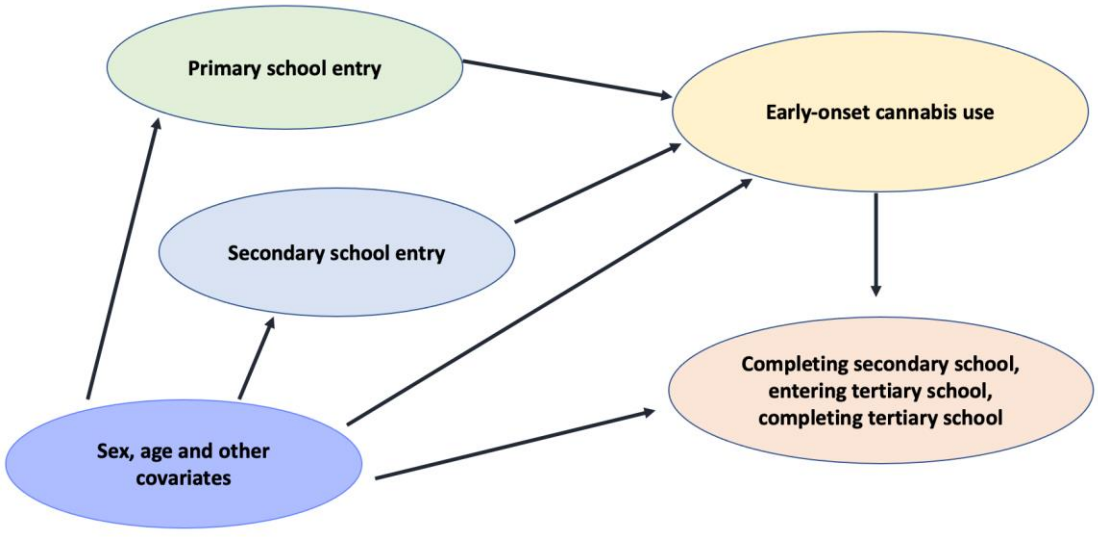
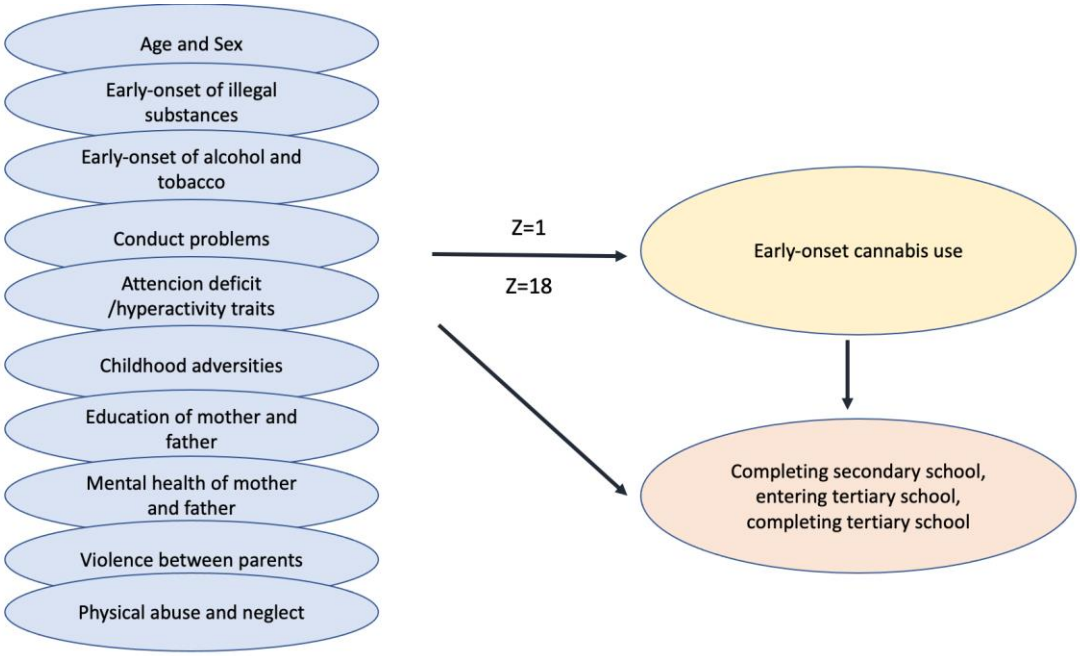


Figure 5 DAG cartoon to depict the possibility of a single confounding variable



As explained below, there are multiple potential confounding variables of the type depicted in Figure 6, which can be arranged as a vector that runs from the first suspected confounder (subscript z=1) to the last suspected confounder (subscript z=Z) as shown in the figure. Estimation of cannabis-attributable disruption of education has been completed with due attention to each of the potentially confounding variables in this vector from z=1 to z=18, in a series of multiple regression analyses, with an acknowledgment that in actuality there might be z=18+1 through z=Z omitted variables that represent misspecifications of the model and sources of residual or unexamined confounding.

Figure 6 Potential confounding variables



Whereas some of these omitted variables can be regarded as individual-level sources of variation in an individual's educational trajectory (e.g., educational attainment values of the maternal and paternal grandparents; other familial investments in the educational success of the individual child), many of these omitted variables may be regarded as characteristics of a local

area or a country. For example, in some (but not all) jurisdictions, children are required by law to be in school until a specified legal school leaving age. Within countries, there can be variations in the school leaving age across sub-national jurisdictions. Concurrently, in some (but not all) jurisdictions, there is a pattern of uneven penalties and uneven enforcement of the international psychotropic drug conventions that make cannabis an internationally regulated illegal drug (e.g., Lansing versus Ann Arbor within Michigan). Supra-individual sources of variation of this type can be difficult to specify and to model in empirical research. Nonetheless, for this dissertation research project, the conditional form of the logistic regression model has been used to hold constant sources of local area variation of this type, via matching. The nature of the conditional logistic regression model, and the matching on local area characteristics, is explained below in Section 3.1.1 of this chapter.

It is noteworthy that the validity of estimates from the multiple regression model can be challenged when there is unspecified heterogeneity in the cannabis estimates (e.g., appreciable qualitative or quantitative variation in the cannabis estimates across subgroups or levels of the potentially confounding variables), the multiple regression model has been extended as shown in Figure 9, where the DAG of Figure 7 has been amended to convey the possibility of such heterogeneity, which also has been probed using multiple regression analyses.

The resulting series of multiple regression analyses, completed for each of the educational outcomes specified in the dissertation project's research aims, produces a mosaic of estimates, each of which conveys the degree to which early-onset cannabis smoking might account for disruption of educational trajectories. In most dissertation research projects of this type, the resulting mosaic would be specific for an individual state within a country, or might be based upon analyses of data from an epidemiological survey of a nationally representative probability sample

of area residents. In this dissertation research project, the mosaic has been enriched by assembling epidemiological survey data from multiple countries, and by completing the multiple regression analyses for all of these countries. Whenever possible, estimates have been produced for each country to enable the use of meta-analysis approaches to plot the resulting estimates and to derive summary estimates with due attention to the heterogeneity of the estimates.

The multi-country character of this dissertation research project has been made possible by drawing upon the work of the World Health Organization World Mental Health Surveys Consortium (WHO/WMHS), which was organized to improve estimates of Disability-Adjusted Life Years (DALYs) and other information required for a new iteration of the Global Burden of Disease (GBD) project. As described below, the WMHS required completion of nationally representative sample surveys in each of the participating countries; in a subset of the countries, it was a similarly drawn representative probability sample in a designated area, such as the metropolitan areas of Beijing and Shanghai in China. Professor Ronald Kessler of Harvard University, who is the overall Principal Investigator, and the Principal Investigators (PI) in each WMHS country agreed to make the WMHS survey data available for completion of the novel analyses and interpretation required for this dissertation research, under guidance and supervision of my primary dissertation advisor, Professor Jim Anthony of Michigan State University. As noted in the preface, I am grateful to be the recipient of this valuable data from what has become an important early 21st century 'classic study' in psychiatric epidemiology.

In aggregate, the WMHS covers all world regions designated by the World Health Organization, and before it is completed, the initiative will encompass survey data from more than 25 countries. At the time of launching this dissertation research project, there was coverage of 16 countries as mapped in Figure 7: seven countries in Europe (France, Belgium, Italy, Germany,

Netherlands, Spain, and Ukraine), three from the Americas (Colombia, Mexico, and the United States), two from the Middle East (Lebanon and Israel), two from Africa (Nigeria and South Africa) and two from Asia (China and Japan). It should be noted that it was possible to hold constant the local area sources of variation, via matching, for all of these countries, but the degree of control over individual-level sources of variation depended upon the measurement plan in each country. As explained below, some of the potentially confounding variables z=1 through z=18 were assessed in some countries, but not in others. This chapter explains this variation. The presentation of results in later chapters will provide additional details about covariate control, and the unevenness of covariate control will be mentioned as one of the limitations of the study in the dissertation's discussion chapter.

Figure 7 The 16 WHMS participating countries

There are detailed descriptions of the WMHS methods and approach in edited books and multiple journal articles, which served as source materials for this dissertation research project. This chapter provides a succinct overview of these methodological details, gained by reading the source materials and via consultation with the dissertation advisor (Dr. James C. Anthony), who has been a collaborator in the WMHS Consortium and has attended its annual collaborators meeting since 2001, through which these details of methods were refined. The primary WMHS source materials consulted for this dissertation research project were: *The WHO World Mental Health Surveys* by Kessler & Ustun Ed. (2008), *The National Comorbidity Survey Replication (NCS-R): background and aims* by Kessler & Merikangas (2004), *The US National Comorbidity Survey Replication (NCS-R): design and field procedures* by Kessler et al. (2004), *Prevalence, Severity, and Unmet Need for Treatment of Mental Disorders in the World Health Organization World Mental Health Surveys* by The WHO World Mental Health Survey Consortium (2004), Toward a global view of alcohol, tobacco, cannabis, and cocaine use: findings from the WHO World Mental Health Surveys (Degenhardt et al. 2008). Table 1 provides a summary of each country's WMHS study population, epidemiological sample, and research approach, based primarily upon Kessler & Ustun´s book (Ronald C. Kessler and Ustun 2008).

Table 1. World Mental Health Survey sample characteristics. Data from the first 16 participating sites of the World Mental Health Survey Consortium, 2002-2007.

Region/Country		Survey[a]	Years	Participation level (%)	Sample Size	Age ranges
Americas						
	Colombia	NSMH	2003	87.7	4426	18-65
	Mexico	M-NCS	2001-02	76.6	8526	18-65
	United States	NCS-R	2002-03	70.9	5692	18 and older
Europe						
	Belgium	ESEMeD	2001-02	50.6	2419	18 and older
	France	ESEMeD	2001-02	45.9	2894	18 and older
	Germany	ESEMeD	2002-03	57.8	3555	18 and older
	Italy	ESEMeD	2001-02	71.3	4712	18 and older
	Netherlands	ESEMeD	2002-03	56.4	2372	18 and older
	Spain	ESEMeD	2001-02	78.6	5473	18 and older
Middle East and Africa						
	Ukraine	CMDPSD	2002	78.3	4725	18 and older
	Israel	NHS	2003-04	72.6	4859	21 and older
	Lebanon	LEBANON	2002-03	70.0	2857	18 and older
	Nigeria	NSMHW	2002-04	79.3	6752	18 and older
	South Africa	SASH	2002-03	87.1	4351	16 and older
Asia						
	Japan	WMHJ	2002-07	51.4	3417	20 and older
	People's Republic of China	B-WMH, S-WMH	2002-03	74.7	5201	18 and older

[a] ESEMeD (The European Study Of The Epidemiology Of Mental Disorders); NSHS (Bulgaria National Survey of Health and Stress); NSMH (The Colombian National Study of Mental Health); WMHI (World Mental Health India); NHS (Israel National Health Survey); WMHJ2002-2003 (World Mental Health Japan Survey); LEBANON (Lebanese Evaluation of the Burden of Ailments and Needs Of the Nation); M-NCS (The Mexico National Comorbidity Survey); NZMHS (New Zealand Mental Health Survey); NSMHW (The Nigerian Survey of Mental Health and Wellbeing); NIMHS (Northern Ireland Mental Health Survey); B-WMH (The Beijing World Mental Health survey); S-WMH (The Shanghai World Mental Health Survey); RMHS (Romania Mental health Survey); SASH (South Africa Health Survey); CMDPSD (Comorbid Mental Disorders during Periods of Social Disruption); NCS-R (The US National Comorbidity Survey Replication).

3.1.1. Series of research steps

As outlined in Chapter 2, the original plan for this study was motivated by concern that exposure of the adolescent brain to tetrahydrocannabinol (THC) and other cannabis compounds might have neurotoxic effects (Mechoulam and Parker 2013), as expressed in recent studies and reviews of the literature on cannabis smoking and IQ test performance (Meier et al. 2012). But the research on cannabis-associated IQ deficits faces many methodological problems, as well as issues

of interpretation (e.g., the pragmatic question of what it means when cannabis smokers score a few points lower on an IQ test, as compared to non-smoking peers). For this reason, the outcomes of interest were chosen to be societal expectations about trajectories of schooling, framed so as not to face stringent measurement difficulties in the context of cross-national research (as are faced in cross-national research on IQ test performance). That is, almost everyone can appreciate the practical significance of failing to enter the secondary school level, and failing to earn a high school diploma, as well as failing to enter college at the tertiary level, and dropping out of college before that degree is earned. The trajectory of failure to achieve educational goals that have been set forth by one's family, society, or self is of particular significance and was thought to encompass two outcomes of particular importance to the individual and to society at large -- of greater significance than a few points difference on an IQ test.

Of course, societies differ in their expectations about trajectories of educational attainment, and these expectations are known to show broad country-to-country variations, as well as some within-country variations. An outward manifestation of these expectations will be seen in Chapter 4, where a substantially larger proportion of adults in the United States have entered college and have completed a college degree, as compared to corresponding proportions from the low-to-middle income countries. Within-country variations in these expectations have been illuminated in the studies by Professor Rosa Crum and colleagues, whose work provides evidence of more noxious health effects when non-Hispanic Whites in the United States of America (USA) enter college but fail to complete college, as compared to little or no evidence of noxious health effects when non-Hispanic Blacks in the USA enter college but fail to complete college. Professor Crum has advanced the argument that it has been a great achievement for a Black American to enter

college at all, and that the social-role expectations about failure to finish college are less salient in that context (Crum and Anthony 2000).

This analysis of the situation motivated a cross-national research plan with estimates of cannabis-associated failure to achieve educational goals based on post-stratification matching of study participants within risk sets defined by areas of residence as small as possible to achieve in this context (e.g., counties or county-groups within the USA), so as to constrain socially shared sources of variation in these expectations (e.g., societal norms about school achievement), and to allow individual-level or behavioral sources of variation to be seen more prominently (e.g., see (Crum and Anthony 2000; Tomas, Vlahov, and Anthony 1990) for a detailed overview of the rationale for local area-matching when the goal is to estimate whether drug use has had an effect on human health). Because there are broad area-related variations in availability and social response to cannabis smoking, the area-matching plan also had advantages because it places some constraints on the degree to which society responds to cannabis smoking more or less punitively. For example, decriminalized cannabis and legal availability in Amsterdam relative to other places in the Netherlands, in Germany versus the Netherlands, or in Colorado and Washington State versus Michigan or Arkansas motivates the use of a generalized linear model with logit link function and a subscripted intercept so as to condition on the area of residence in the estimation process (i.e., 'conditional form of logistic regression' akin to what is used in the estimation of odds ratios in matched pairs data).

The plan also was to control for individual-level sources of variation in school performance, such as childhood conditions of the type mentioned above, which also might be influenced on whether a young person starts to smoke before late adolescence (e.g., Attention deficit hyperactivity disorder –ADHD, harsh or otherwise inept parenting circumstances in the

background, etc. -- see Hui Cheng's work on drinking outcomes in relation to harsh parenting (Cheng, Huang, and Anthony 2011)). Unlike the socially shared sources of variation that can be constrained by local area matching, these individual-level characteristics can be constrained via covariate adjustments in the context of generalized linear modeling.

The originally-conceived analysis plan was modified in order to accommodate feedback from the members of my committee and my mentor. For example, some individuals thought that it might be a problem to have the local area matching and formation of risk sets based upon the study participant's area of residence at the time of survey assessment, as opposed to the area of residence at the time of the early-onset cannabis smoking. Whether this is a serious concern was discussed, and it was noted that virtually all prior case-control studies in cancer and cardiovascular disease research are based on neighborhood-matched cases and non-cases, where the area-matching is based on the area where the cases were diagnosed, and not on the area of residence at the time of exposure. My advisor instructed me not to address these concerns by this 'appeal to authority and past experience' (as exemplified in the just-mentioned studies). Instead, he encouraged me to respond to the challenge with a new cycle of additional analyses that involved breaking up the area-matched risk sets, and the use of the unconditional form of logistic regression in analyses repeated country-by-country, with a meta-analysis approach used to summarize the resulting country-specific estimates.

Another revision of the original analysis plan involved concerns regarding covariate adjustment for adverse circumstances of childhood experience, such as harsh parenting or punishment. Here, my revised plan accommodated the objection by showing regression-based estimates from the conditional logistic regressions with and without covariate adjustment for these circumstances.

In summary, the original plan for the dissertation research project included a statistical analysis that can constrain socially shared sources of variation while making the individual-level sources of variation to arise prominently. In addition to the set of original analyses that satisfies that goal, I accommodate a set of analyses that addressed critics regarding potential biases derived from using as matching variables the place where the individual lives during the time of interview rather than the place where the individual lived at the time of first use of cannabis. Also, I added analysis to control the potential confounder effect of adverse circumstances during childhood experiences such as harsh parenting or punishment.

3.2. Research design

In terms of epidemiological methods, the nature of the WMHS research design is that of a cross-sectional survey of each country's population of community-dwelling residents of adult age, although in some countries, teens in middle adolescence also were sampled. Because the WMHS data collection included standardized assessments to gather age of onset information from each individual participant, it has been possible to organize the analyses as if the data were from a prospective cohort study of suspected drug-attributable hazards. In the estimation of the hypothesized exposure-hazard associations, the 'exposed' members of the cohort are individuals who had started cannabis smoking prior to age 17, and the 'non-exposed' members of the cohort are individuals who had not started smoking cannabis by that age. The suspected cannabis-attributable hazard outcomes of interest are specified in relation to educational milestones, with a particular focus on failing to complete secondary school. Points for later discussion include the possibility that there are constraints on the information value of an observed cross-sectional survey

sample of this type. For example, in a study of hazards associated with injecting drug use (IDU), there might be selection bias in the cross-sectional sample to the extent that IDU can be a potent cause of death (e.g., by drug overdose or due to IDU-attributable infectious diseases). Whether this also is true in research on cannabis-attributable hazards is discussed, and a set of simulation analyses has been completed in order to forecast conditions under which cannabis-associated premature mortality might have influenced the study estimates reported here. Another point of discussion involves the possibility of information bias, such as non-differential or differential misclassification of the exposure variables, which might be expressed in the form of less accurate information about the age of onset of cannabis smoking for poorly educated individuals versus better-educated individuals, or vice versa.

3.3. Study population and sample

At the time this dissertation research project was launched, the WMHS included seventeen epidemiologic surveys in the 16 countries listed in Table 1, with regional representation of the Americas (Colombia, Mexico, and the USA), Europe (Belgium, France, Germany, Italy, Netherlands, Spain, Ukraine), the Middle East and Africa (Israel, Lebanon, Nigeria, South Africa), and Asia (Japan and the People's Republic of China). WMHS projects also have been completed in other countries, such as New Zealand, but either the data were not ready for inclusion in this dissertation research project, or the country-level PI leadership declined to participate. For example, it was thought that the data on educational attainment in New Zealand might not be sufficiently comparable to the data on educational attainment in other countries. For this reason, the New Zealand site is not represented in this project.

In the original WMHS plan, the study population for each country was to be specified in relation to adult inhabitants of non-institutionalized dwelling units (e.g., households), and in most participating countries, the study samples were designed to be nationally representative. In several countries, resource constraints and other considerations narrowed the specification of the study population. For example, in some countries, the study population was specified with respect to the urban population of the country (Mexico and Colombia) or in relation to cities considered to be of particular importance (Japan, Nigeria, The People's Republic of China). In the People's Republic of China, two separate surveys were performed for Beijing and Shanghai. For most countries, the target populations involved non-institutionalized community-dwelling unit residents aged at least 18 years. For Japan, the minimum age for surveyed participants was 20 years, and in Israel, it was 21 years.

In some epidemiological survey projects, it is possible to start with a roster of all citizens of the country and to draw a random sample from that roster (e.g., this can be done in Denmark). In most countries, there is no national roster, and instead, a multi-stage approach is required. In this multi-stage approach, the final sample is obtained after a sequential combination of two types of sampling. First, in the multi-stage approach, there is a probabilistic selection of geographic areas to later, in the last two selection stages, there is a use of registries or population lists from which individuals are finally selected to be invited to participate in the survey.

For the WMHS initiative, the participating countries implemented overall similar probability sampling techniques with some country-specific variations based on local financial, infrastructure, and logistic resource constraints. Israel, Belgium, and Japan used techniques that involved high-quality population rosters from which individuals were directly selected in a probabilistic way. The remaining 13 countries used variants of the multi-stage probability

sampling methods. France, The Netherlands, and Germany implemented a two-stage sample design. France used telephone directories to choose households as the first stage and then selected an adult from the chosen households in a random way. The Netherlands used national postal lists to choose households from which randomly selected individuals. Germany instead selected municipality units as the first sampling stage and then randomly chose adults from each municipality population registry. South Africa, Lebanon, Italy, Ukraine, and The People´s Republic of China implemented a three-stage sampling technique. Italy selected municipality units as the first stage of sampling from which electoral districts were selected as the second stage, and randomly-chosen adults from each district´s population registry were the final stage. Ukraine took a similar approach, but used postal districts as the second stage of sampling before randomly selecting adults from an enumerated list of each district´s residents. The other four countries that used a three-stage sampling technique, i.e., Lebanon, China, Mexico, and South Africa, used as the first stage neighborhood units or census enumeration districts selected before selecting households (second stage) from where adults were randomly selected (third stage).

Finally, for Colombia, Nigeria, Spain, and the United States, a four-stage probability sampling technique was implemented. In the first stage of the sampling sequence, counties or municipal units were selected, from which in turn segment blocks were chosen (second stage), and from those, the dwelling unit was selected as the third stage of the sampling process. The last stage (fourth) involved the selection of the final unit of sampling, i.e., the 'designated respondent' within each dwelling unit.

3.4. Human subjects protection

Prior to conducting the survey assessment with each sampled designated respondent (DR), it was necessary to seek and obtain the DR's informed consent for participation. For this purpose, the DR was provided with a copy of an informed consent and study disclosure form, which was read to the DR, and the DR gave written or oral consent according to the study protocol approved by the cognizant institutional review board (IRB) or committee responsible for the protection of human subjects in each country. The appendix materials of the dissertation include the informed consent and disclosure statements used in the United States WMHS

(http://www.hcp.med.harvard.edu/ncs/).

3.5. Assessment strategy

Once informed consent was obtained, the assessment plan involved a face-to-face interview with each DR in a private location in or near the dwelling unit, using either a computer-assisted personal interview (CAPI) or the conventional 'Paper-And-Pencil Interview' (PAPI) version of the WHO Composite International Diagnostic Interview specifically designed for the purpose of the WMH Survey Initiative. Both versions (CAPI and PAPI) of the interview schedule are available on the WMHS web site http://www.hcp.med.harvard.edu/wmhcidi/.

The WMHS initiative used the World Health Organization Composite International Diagnostic Interview, version 3.0 (WMH-CIDI), to gather information from DRs in all participating countries. WHO standard procedures were used to translate the WMH-CIDI instrument and the training materials into the main local languages, which for some countries

constituted translations to more than one language. For example, in Nigeria, the instruments were translated into Yoruba, Hausa, Igbo, and Efik. In most countries, the process involved translation, back-translation, and harmonization, as described by Harkness et al. (Harkness et al. 2008).

The WMH-CIDI can be described as a highly standardized 'interview schedule' with a fixed sequence of modules about a broad range of topics that include demographic information, physical and mental health history, and meaningful life events. Each module consists of a fixed sequence of standardized questions, almost always with pre-coded response categories. The interviewer (or computer) presents the same questions in the same sequence within each module.

To reduce survey costs, respondent burden, and the length of the assessment, each participating country was allowed to separate CIDI modules into two (or more) parts. The Part 1 assessment modules, which covered demographic information, screening questions, and core psychiatric disorders thought to be of primary importance, were administered to all participants. The Part 2 assessment modules were administered to a probability subsample of the Part 1 participants, which may be analyzed as a probability sample of all Part 1 participants, enriched by 100% sampling of Part 1 participants with Part 1 screening evidence suggestive of psychiatric disorders covered in Part 2, or as a 100% sampling of Part 1 participants with Part 1 screening evidence suggestive of psychiatric disorders, plus a 25% random sample of all other Part 1 participants. In order to take into account these variations in the probability of being selected for Part 2, the general analysis weight for Part 1 analyses needed to be amended. The first Part 1 weight is based on the probability of selection and post-stratification adjustments. In contrast, the Part 2 weight takes into account the probability of selection into Part 2, as well as the Part 1 analysis weight.

An illustration of between-country variations in the assessment strategy may be helpful. In Mexico, Colombia, Israel, and South Africa, it was decided that the module on drug dependence and related problems should be included in CIDI Part 1. In the other WMHS countries, this drug dependence module was included in Part 2. Table 1 reviews the country-by-country placement of the various CIDI modules in Part 1 and Part 2.

Section 3.6 provides a detailed overview of each study variable used in this dissertation research project. In brief, these WMH-CIDI variables include the DR's sex, age, and the number of years of formal education completed by the time of the interview. In addition, the WMH-CIDI assessments provided information about the use of tobacco, alcohol, and the internationally regulated drug (IRD) compounds, some of which are 'illegal' in most parts of the world (e.g., LSD), whereas others may be used medicinally (e.g., cannabis, cocaine, heroin, MDMA). To address the variations in which drugs are illegal and which are illegal, we refer to alcohol and tobacco (which are not internationally regulated), and separately we refer to internationally regulated drugs (IRD), as listed under the United Nations international conventions for control of 'narcotic drugs' (1961, http://www.incb.org/pdf/e/conv/convention_1961_en.pdf) and of 'psychotropic drugs' (1971, http://www.incb.org/pdf/e/conv/convention_1971_en.pdf). In addition, for most countries, Part 2 of the WMH-CIDI provides information about childhood characteristics and adverse events that might affect both drug involvement and education attainment: a history of hyperactivity, inattention and conduct problems, as well as a history of having suffered child maltreatment (physical or neglect), parental absence (because of death, divorce or other cause), family violence or family economic problems, and parental mental disorders, drug use, or antisocial traits.

3.6. Study variables

In this study, there are two key variable categories: the set of variables that are informative about the individual's educational attainment and the set of variables that are informative about the cannabis use history.

3.6.1. Educational attainment variables

This set includes 5 variables:

1) General educational level

2) Failing to enter into primary school (FEPS)

3) Failing to complete secondary school (FCSS)

4) Failing to enter into tertiary school (FETS)

5) Failing to complete tertiary school (FCTS)

All these variables were built from one of the two versions of a unique WMH-CIDI question in a Part 1 module. For China, Ukraine, Nigeria, Lebanon, Israel, and the countries of Europe, the version of the question used was the following:

How many years of school have you completed? (IF NEC: Please include any years of higher education). The answers included:

The actual number =____ years

98 = Don´t know

99 = Refused

For the United States, Colombia, Mexico, and Japan, a slightly different question was asked:

What is the highest grade of school or year of college you completed?

The standardized response options included the following categories: 0=none; 1=one; 2=two; 3=three; 4=four; 5=five; 6=six; 7=seven; 8=eight; 9=nine; 10=ten; 11=eleven; 12=twelve; 13=thirteen; 14=fourteen; 15=fifteen; 16=sixteen; 17=seventeen or more; 98= don´t know; 99=refused.

Given that educational programs vary across countries regarding the age of school entry and duration of each of the schooling levels, the raw information about completed years of formal education was standardized to make possible comparisons across countries. This standardization was performed using information regarding the characteristics of each site educational system provided by each principal investigator. Thus, it was possible to specify a 7-level variable that contains the educational information of each site in a way that is consistent across countries.

The resulting 7-level variable, which is the "general educational level" variable for this study, includes all the internationally recognized levels of education and milestones:

1= No formal education

2=Some primary

3=Complete primary

4=Some secondary

5=Complete secondary

6=Some tertiary school

7=Complete tertiary school or more

The next variable accounts for failing to enter into primary school (FEPS) and is built from the general educational level variable. The FEPS variable is dichotomous and gets a value of zero if the individual achieved entry into primary school (i.e., a value of 2 or higher in the general education level variable), and a value of 1 if the person failed to have at least some primary school (i.e., a value of 1 in the general education level variable).

The variable that accounts for failing to complete secondary school is also built from the general educational level variable. It is dichotomous and gets a value of zero if the individual completed secondary school (i.e., a value of 5, 6 or 7 in the general education level variable), and a value of 1 if the person failed to complete secondary school (i.e., a maximum value of 4 in the general education level variable).

Likewise, the variable that accounts for failing to enter into tertiary school is dichotomous and built from the same general educational level variable. The FETS variable gets a value of zero if the individual has some tertiary school (i.e., a value of six or 7 in the general education level variable), and a value of 1 if the person has only completed secondary school (i.e., a maximum value of 5 in the general education level variable).

Finally, failing to complete tertiary school variable has a value of zero if the individual has completed tertiary school (i.e., a value of 7 in the general education level variable), and a value of

1, if the person has not (yet) completed tertiary school (i.e., a maximum value of six in the general education level variable).

3.6.2. Cannabis use category variables

This set includes two variables:

1) History of cannabis smoking

2) Early-onset cannabis use

The variable on ‘history of cannabis use’ is a categorical one that combines the information about ever use of the substance and information about the age of onset of that use. To build this variable, the author used the information drawn from two of the original WMH-CIDI questions:

The first one is: *Have you ever used either marijuana or hashish, even once?* This question had as answer options the following:

1=Yes

5=No

8=don´t know

9=Refuse

And the second one is: *How old were you the first time you used (marijuana/hashish)? IF "AS LONG AS I CAN REMEMBER," PROBE: Was it before your teens? IF NOT YES, PROBE: Was it before your twenties?*

The responses were coded as follow:

The actual number < 100 _____ YEARS OLD

12=BEFORE TEENS

19=BEFORE TWENTIES

998=DON´T KNOW

999=REFUSED

The history of cannabis smoking is zero if the individual never used cannabis, 1 if the user started at age sixteen or later, 2 if the user started between ages six and 16 years, and 3 if the onset of use was at any age before age six years. Missing values for the history of the cannabis smoking variable were adjudicated when either the cannabis ever use or the age of onset questions had missing values, ´don´t know,´ or ´refuse´ values. For most countries, the percentage of missingness for the age of onset variable was less than 1% of those who were cannabis ever users, except for South Africa. In fact, in this country, there were 30 (approximately 10%) of the 288 ever users of cannabis for whom the variable age of onset had missing values.

Also, the reader should note that to reduce the number of missing values because of individuals who did not recall the exact age at which they used the drug for the first time, the WMH-CIDI instrument makes an extra effort to gather that information through two consecutive

follow-up questions: *"Was it before your teens?",* in which case the response was coded 12, or followed by the question *"was it before your twenties?"* if the respondent does not say yes to the previous question, in which case the response was coded as 19.

Early-onset cannabis use was also built from the combined information gathered from the WMH-CIDI questions about cannabis ever use and age of onset. Specifically, the early-onset cannabis use variable is a dichotomous variable coded 1 if the use of the drug started before age 17 years, and coded zero if the respondent has not used cannabis by the time of the interview or if the respondent´s use started at age 17 years or later.

It is worth mentioning that, given that the dataset does not allow disentangling who among those who coded 19 as the cannabis age of onset in the dataset were people who remembered accurately the age they started cannabis and who did not remember it exactly but said it was before their twenties, it is not possible to control or trackback the possibility of misclassification for those who started cannabis any time between age 13 and age 16 years but allocated between those who said started at age 19 and thus not being among the early-onset cannabis users.

3.6.3. Covariates under study

For aims 1 and 2, which are focused on the estimation of the overall association between different schooling and cannabis smoking histories, the only covariates of interest are sex and age.

Sex is a dichotomous variable based upon the observation of the interviewer and coded 1 if the respondent is a male and 0 if it is a female.

Age is a continuous variable coded with the actual number of years the respondent gives when asked for his or her age. Higher-order polynomials (e.g., age squared) also have been explored.

For aim 2 and 3, sixteen covariates were of interest, including:

Conduct problems during childhood or adolescence

The WMH-CIDI places four questions in the screening instrument administered during Part 1 of the survey to assess conduct problem traits:

The first question is: *Did you ever have a period lasting six months or longer during your childhood or adolescence when you frequently did things that got you in trouble with adults such as losing your temper, arguing or talking back to adults, refusing to do what your teachers or parents asked you to do, annoying people on purpose, or being touchy or irritable?*

The responses were coded as follows:

1= YES

2= NO

8= DON'T KNOW

9= REFUSED

The second question is: *Many children and teenagers go through periods when they do things adults don't want them to do, like lying, stealing, or breaking rules. Did you ever go through a period during your childhood or teenage years when you did any of these things?*

The responses included:

1= YES

2= NO

8= DON'T KNOW

9= REFUSED

The third question asks: *Did you ever go through a period as a child or teenager when you either broke into cars, set fires, or destroyed property on purpose?*

The responses included:

1= YES

2= NO

8= DON'T KNOW

9= REFUSED

And the fourth question is: *When you were a child or a teenager, did you ever run away from home, or repeatedly play hooky from school, or often stay out much later at night than you were supposed to?*

The responses included:

1= YES

2= NO

8= DON'T KNOW

9= REFUSED

Not all the countries administered all these questions in the same manner as the United States, Colombia, Mexico, and Japan, where all four questions were asked. In the case of the

WMHS European participating countries, i.e., Belgium, France, Germany, Italy, the Netherlands, and Spain, only the first one of the questions was asked, but not the other three. In Ukraine, Nigeria, South Africa, and China, only the first and second questions were asked, while in Lebanon, the fourth question was added to the first two questions. Israel did not include any of these questions in its screening questionnaire.

Given that there are differences across countries in how conduct-problems traits were measured, for this study, a different variable was built for each pattern of conduct problem screening questions. Thus, for those countries where all the four questions were asked of the participants, the conduct problem variable coded 1 if at least one of the 4 questions was answered YES, and coded 0 if all the questions were answered with 5. All "Don´t know" and "Refused" answers were turned to missing values. Another conduct problem variable was built for those countries that used just three questions, using the same coding of 1 if at least one of the three questions was answered YES, 0 if all the questions were answered with 5, and missing if the answer was "Don´t know" or "Refused." For those countries that asked two screening questions for conduct problems, a third conduct problem variable was built using the two questions and the same coding system. A similar coding procedure was performed for Lebanon, in which there was just one screening question for conduct problems during childhood or teenage years.

Attention deficit and hyperactivity traits

Attention problems and hyperactivity during childhood or teenage years are assessed with two questions.

The first question is focused on concentration problems that usually start before the age of seven, including problems such as *not being able to keep the mind on what you were doing, losing*

interest very quickly in games or work, trouble finishing what you started without being distracted, and not listening when people spoke to you. During your first years at school—say between the ages of 5 and 7 -- was there ever a period lasting <u>six months or longer</u> when you had <u>a lot more trouble</u> with problems of this sort than most children?

The response options were the following:

1 = YES

5 = NO

8 = DON'T KNOW

9 = REFUSED

The second question is focused on hyperactivity: *Some young kids are very restless and fidgety and so impatient that they often interrupt people and have trouble waiting their turn. Did you ever have a time before the age of seven lasting <u>six months</u> or longer in your childhood when you were like that?*

The responses were coded as:

1 = YES

2 = NO

8 = DON'T KNOW

9 = REFUSED

Most countries used the same question structure for these two questions. However, there was an exception for the six European countries, where the question about concentration problems was worded slightly differently to be focused on age 6 to 10 years instead of 5 to 7 years, as it is

the case for the remaining ten countries: *The next few questions are about problems that usually start in childhood or adolescence. During your first years at school -- say between the ages of six and 10 -- was there ever a period lasting six months or longer when you had a lot more trouble than most children with concentration or attention -- such as not being able to concentrate or keep your mind on what you were doing, losing interest very quickly in games or work, trouble finishing what you started without being distracted, or not listening when people spoke to you?*

Israel did not include questions that screened for attention problems and hyperactivity.

Thus, this study´s attention deficit and hyperactivity trait variable was built using the two previously described questions, being coded 1 if any of the two questions was answered YES and 0 if all the questions were answered NO. Answers like "don´t know" or "refuse" were deemed as missing values.

Early-onset of cocaine

Early-onset cocaine use was built from the combined information gathered from the WMH-CIDI questions about cocaine ever use and the age of onset of the use of that drug. Specifically, Early-onset cocaine use variable is dichotomous and coded 1 if the use of the drug started before age 17 years, and coded zero in any of these two circumstances: the respondent has not used cocaine by the time of the interview or if the respondent´s use started at age 17 years or later.

As was the case with cannabis, the dataset does not distinguish between those coding 19 as the age of onset of cocaine because they did not remember the exact age of onset but said the use started before their twenties from those who remember it. So, there is the possibility of misclassification for those who started cocaine any time between age 13 and age 16 years and thus

not mistakenly allocated among the early-onset cocaine users. This is also true for early-onset users of other illegal drugs and extra medical users of prescription drugs.

Early-onset prescription drugs extramedical use (EOPDU)

The EOPDU variable was built from the WMH-CIDI questions asking about the ever use of prescription drugs without a medical recommendation and the age in which such use started. Specifically, EOPDU variable is dichotomous and coded 1 if the use of the prescription drug started before age 17 years, and coded zero otherwise, i.e., the respondent has never used extramedical prescription drugs by the time of the interview, or the respondent´s use started at age 17 years or later.

Early-onset of other illegal drugs use (EOIDU)

If the respondent started to use heroin, opium, glue, LSD or peyote before age 17, then the EOIDU was coded 1. If the respondents have never used such drugs, or they started to use them at age 17 years or later, then the EOIDU was coded zero.

Having lived with both biological parents up to age sixteen

For all the countries, this variable was derived from the question: *Did you live with both of your biological parents up until you were sixteen?* The responses to this question were coded as:

1 = YES

2 = NO

8 = DON'T KNOW

9 = REFUSED

For Israel, there was a small difference in the response options that participants have for this question. Specifically, in the Israel case, the response options were:

1 = YES

2 = NO, LIVED WITH MOTHER ONLY

3 = NO, LIVED WITH FATHER ONLY

4 = NO, DID NOT LIVE WITH ANY

8 = REFUSED

9 = DON'T KNOW

Thus, taking into account both versions for this question, this study´s variable about living with both parents up to age 16 was coded 1 if the answer was YES, and coded 0, otherwise. "Don´t know" and "Refused" are deemed as missing values.

Having been away from home at least six months

All the countries included this question in their respective surveys: *Up until you were sixteen, were <u>you</u> ever away from home for six months or longer – either in foster care, with other relatives, in a boarding school, hospital, juvenile detention center, or elsewhere? Before the interviewer recoded the response, he or she was prompted with the following statement: CODE "NO" IF R VOLUNTEERS "RETURNED HOME ON WEEKENDS" OR OTHER OCCASIONS DURING SIX-MONTH PERIOD.*

Responses to this question included the following codes:

1 = YES

5 = NO

8 = DON'T KNOW

9 = REFUSED

This variable was recoded to a dichotomous one, where the code 1 continued to represent a YES answer and 0 to a NO answer. "Don´t know" and "Refused" were deemed as missing values.

Years of education of the female head of household

The WMHS instrument for childhood events poses questions about the years of education of the female who was the head of the household for most of the participant´s childhood, irrespective of whether this female was the participant´s biological mother or someone else. The actual question was the following:

How many years of school did (the female head of your household for most of your childhood / your mother) complete?

The responses to this question could be:

A number < 100 _____ YEARS OLD

98 = DON'T KNOW

99 = REFUSED

For this study, this variable was recoded to have a maximum of education years up to 30. This means that any answer greater than 30 was coded as 30. "Don´t know" and "Refused" answers were turned into missing values.

Years of education of the male head of household

Similarly, there is a question about the years of education of the male who was the head of the household for most of the participant´s childhood, irrespective of whether this person was the participant´s biological father or someone else in the family. The actual question was the following:

How many years of school did (the man head of your household for most of your childhood/ your father) complete?

The responses to this question could be:

A number < 100 _____ YEARS OLD

98 = DON'T KNOW

99 = REFUSED

As with the female head of the household´s education variable, this variable for the male head of the household was recorded to have a maximum of education years up to 30. This means that any answer greater than 30 was coded as 30. "Don´t know" and "Refused" answers were also turned into missing values.

Violence between parents

The WMHS assessed the possibility that the participant had witnessed violence between parents or persons who raised the participant. This circumstance was recorded through the following question: *How often did (your parents/the people who raised you) do any of these things (PUSHED, GRABBED, SHOVED, THREW SOMETHING, SLAPPED OR HIT) <u>to each other</u> while you were growing up -- (often, sometimes, rarely, or never)?*

1 = OFTEN

2 = SOMETIMES

3 = RARELY

4 = NEVER

8/5 = DON'T KNOW

9/6 = REFUSED

All countries but Israel asked this question.

This variable was recoded to a 3-level categorical variable where "Often" was coded as 1, "Sometimes" coded to 2, and "Rarely" or "Never" to 0. "Don´t know" and "Refused" were deemed as missing values.

Physical abuse

To explore experiences that the participant may have had during childhood, the WMHS instrument places this question: *When you were growing up, how often did someone in your household do any of the things (PUSHED, GRABBED OR SHOVED. THREW SOMETHING.SLAPPED OR HIT) <u>to you</u> – often, sometimes, rarely, or never?*

The responses to this question include:

1 = OFTEN

2 = SOMETIMES

3 = RARELY

4 = NEVER

8 = DON'T KNOW

9 = REFUSED

This variable was recoded to a 3-level variable where “Often” was coded 1, “Sometimes” coded as 2, and “Rarely” and “Never” coded as 0. “Don´t Know” and “Refused” were deemed as missing values.

Neglect

The WMH-CIDI asks five separate questions to assess the neglect that the respondent may have experienced during childhood. These five questions were placed only for Colombia, Mexico, the United States, Ukraine, Lebanon, Nigeria, China, and Japan. In the European countries, Israel and South Africa, the CIDI modules did not ask these questions.

A summary “neglect” variable was built from the following WMH-CIDI questions a) *How often were you made to do chores that were too difficult or dangerous for someone your age?* b) *How often were you left alone or unsupervised when you were too young to be alone?* c) *How often did you go without things you need like clothes, shoes, or school supplies because your parents or caregivers spent the money on themselves?* d) *How often did your parents or caregivers make you go hungry or not prepare regular meals?* And, e) *How often did your parents or caregivers ignore or fail to get you medical treatment when you were sick or hurt?*

All of these questions had responses, such as:

1=OFTEN

2=SOMETIMES

3=RARELY

4=NEVER

8 = DON’T KNOW

9 = REFUSED

Therefore, this study´s "neglect" variable was coded 1 if any of the five questions were answered as "Often" or "sometimes," and coded as 0 if all questions were answered as "Rarely" or "Never." "Don´t know" and "Refused answers were deemed as missing values.

Mental health problems in the parenting female

This variable summarizes the information that the DR gave about having witnessed clinical features or signs associated with depression, anxiety, mania, drug-related problems, or suicidal intent in the woman who raised her or him. The WMH-CIDI questions that assess those issues involved the following:

A) During the years you were growing up, did (WOMAN WHO RAISED R) ever have periods lasting 2 weeks or more where she was sad or depressed most of the time?

The responses to this question included:

1= YES

2 = NO

8 = DON'T KNOW

9 = REFUSED

B) During the time you were growing up, did (WOMAN WHO RAISED R) ever have periods of a month or more when she was constantly nervous, edgy, or anxious?

The responses to this question included:

1= YES

2 = NO

8 = DON'T KNOW

9 = REFUSED

C) Did (WOMAN WHO RAISED R) ever complain about anxiety attacks where all of a sudden she felt frightened, anxious, or panicky?

The responses to this question included:

1= YES

2 = NO

8 = DON'T KNOW

9 = REFUSED

D) Did (WOMAN WHO RAISED R) ever have a problem with alcohol or drugs?

The responses to this question included:

1= YES

2 = NO

8 = DON'T KNOW

9 = REFUSED

E) Did (WOMAN WHO RAISED R) ever attempt to commit suicide?

The responses to this question included:

1= YES

2 = NO

8 = DON'T KNOW

9 = REFUSED

There are two differences across countries that should be noted. First, none of these questions were placed in the Israel survey; and second, instead of using only one question as in the rest of the countries, in the six European countries, there were three separate questions for parenting female´s alcohol and drug use problems. Thus, this information was gathered using these three questions: a) *Did (WOMAN WHO RAISED R) ever have a problem with drinking?* b) *Did she ever abuse prescription drugs such as valium, sleeping pills, or diet pills?* And, c) *Did she ever have a problem with illegal drugs?* However, the response alternatives remained the same.

Therefore, with the information gathered from these five questions, this study´s "mental health problems in the parenting female" variable was coded 1 if any of the five questions were answered as "yes," and coded as 0 if all questions were answered as "no." "Don´t know" and "Refused" answers were deemed as missing values.

Mental health problems in the parenting male

Similarly, the information about clinical features or signs associated with depression, anxiety, mania, drug-related problems, or suicide intent in the man who raised the respondent was gathered from the following WMH-CIDI questions:

A) During the years you were growing up, did (MAN WHO RAISED R) ever have periods lasting 2 weeks or more where he was sad or depressed most of the time?

The responses to this question included:

1= YES

2 = NO

8 = DON'T KNOW

9 = REFUSED

B) During the time you were growing up, did (MAN WHO RAISED R) ever have periods of a month or more when he was constantly nervous, edgy, or anxious?

The responses to this question included:

1= YES

2 = NO

8 = DON'T KNOW

9 = REFUSED

C) Did (MAN WHO RAISED R) ever complain about anxiety attacks where all of a sudden, he felt frightened, anxious, or panicky?

The responses to this question included:

1= YES

2 = NO

8 = DON'T KNOW

9 = REFUSED

D) Did (MAN WHO RAISED R) ever have a problem with alcohol or drugs?

The responses to this question included:

1= YES

2 = NO

8 = DON'T KNOW

9 = REFUSED

E) Did (MAN WHO RAISED R) ever attempt to commit suicide?

The responses to this question included:

1= YES

2 = NO

8 = DON'T KNOW

9 = REFUSED

Similar to the questions for the parenting female, in Israel, none of these questions for the parenting male were asked. Another difference across countries was that in the six European countries, there were also three questions about the parenting male´s alcohol and drug use problems. For the rest of the countries, it was a single question. Thus, in the same way, as for the parenting female, the information about mental health problems for the parenting male in the six European countries was gathered using these three questions: a) *Did (MAN WHO RAISED R) ever have a problem with drinking?* b) *Did he ever abuse prescription drugs such as valium, sleeping pills, or diet pills?* And, c) *Did he ever have a problem with illegal drugs?* However, the response alternatives remained the same.

Finally, this study´s "mental health problems in the parenting male" variable was coded 1 if any of the five questions were answered as "yes," and coded as 0 if all questions were answered as "no." "Don´t know" and "Refused" answers were deemed as missing values.

Early-onset alcohol use (EOAU)

This variable comes from a single question in the WMH-CIDI instrument: *The next questions are about your use of alcohol. How old were you the very first time you ever drank an alcoholic beverage – including either beer, wine, a wine cooler, or hard liquor?* Thus, early-onset

alcohol use was coded as "1" if the use of the substance started by age 16 or earlier. It coded zero if the respondent has not used alcohol by the time of the interview, or if the onset was by age 17 or later.

For this variable, I took into account that all the countries, except the USA and Japan, asked the alcohol use question to all participants (i.e., as it was in PART 1). In Japan and the USA, the substance use instrument was in PART 2. Also, note that for Israel, the questionnaire included a gate question about the use of alcohol. If the respondent answered positively, then he was asked about the following age of onset question.

Early-onset tobacco use (EOTU)

WHM participating countries gathered in different ways information about tobacco use. Because of that, the raw data were standardized to have a cross-country variable for the age of onset, which allowed me to build the early-onset tobacco use variable. Some aspects are noteworthy at the front in this step. First, the European countries (except Ukraine) and Japan did not ask the question of the age of onset of tobacco. Second, the age of onset of tobacco use was asked in PART 1 of the survey for Colombia, Mexico, and South Africa, while for the rest of the countries was asked in PART 2. Lastly, for quality control purposes, I built the variable of tobacco ever-use for each country from the age-of-onset tobacco variable. Effectively, I achieved to replicate the results found by Degenhardt et al. (2008).

Thus, if the respondent started to use tobacco (cigarette, cigar, or pipe) before age 17, then the EOTU was coded 1. if the respondents have never used tobacco, or they started to use them at age 17 years or later, then the EOTU was coded zero.

3.7. Analytic plan

3.7.1. The conditional form of multiple logistic regression

Section 3.1 and this section of the dissertation research report refers to a conditional form of multiple logistic regression, which also is known as a 'fixed effects' model in the family of 'generalized linear models' with a logit link function. Written in the form of an equation that can be found in many epidemiology and statistics textbooks, including Breslow and Day (Breslow and Day 1980), the model expresses the expected value of the response variable, Y, as a function of a K sub-scripted intercept, where the sub-script runs from 1 to K, and where K is the number of risk sets within which at-risk individuals have been matched, and one or more explicitly measured covariates, Xz where the z subscript runs from 1 to 18 and stands for one or more covariates in the model:

Figure 8 Multiple regression model

$$\log\left(\frac{p}{1-p}\right) = \alpha_k + \sum \beta_i x_{i^z}$$

3.7.2. Aim-by-aim explanation of approach

For AIM 1, to estimate crude and covariate-adjusted cross-sectional associations that link a history of any cannabis smoking with school entry, as well as to estimate the degree to which entry into primary school might account for or simply predict EOCU, with due attention to background characteristics (sex, age).

Frequency tables and estimated proportions were used to study the occurrence of cannabis use- related variables, including categories of age of onset of cannabis use and early-onset cannabis use, and to study schooling-related variables including failing to enter into primary school.

Conditional logistic regression for local area matched sets was used to assess the association between age-of-onset based categories of cannabis use and failing to enter into primary school. Crude or unadjusted OR (uOR) and adjusted OR (aOR) were estimated. The aOR was estimated by holding constant sex and age as exogenous covariates.

Conditional logistic regression was used for two reasons:

First, the sample size of people failing to enter into primary school was very small for most of the countries, which imposed difficulties for modeling the association with cannabis use within each country in a separate way. Under the initial assumption that the strength of association is relatively homogeneous across countries, the conditional logistic regression approach allows one to borrow information across countries.

Second, conditional logistic regression is an example of an appropriate 'fixed effects' regression model for local area matched sets of WMHS participants (i.e., with matching people by area of residence at the time of the interview). As explained in Section 3.1, the use of this approach helps to constrain socially shared local area characteristics that might influence educational and drug use trajectories such as differences in school leaving age, drug availability, law enforcement, and other sociocultural characteristics that might function as confounding variables when estimating the association between schooling and cannabis use trajectories not only across countries but also across different areas within countries.

Additionally, given that there are people who recorded 0 to 5 years as their age of onset of cannabis use, in the post-estimation exploration analysis, separate estimates of association were calculated: one in which all early-onset cannabis users were included, and another in which those who started at age 5 years or earlier were excluded.

For AIM 2, to estimate the strength of association between levels of schooling and onset of cannabis before age 17, with due attention to potentially important subgroup variations (e.g., sex, age).

As performed for Aim 1, a conditional logistic regression is implemented to accomplish Aim 2, matching individuals by geographical areas of residence to estimate the crude and the age-and-sex adjusted association between EOCU and levels of schooling.

Three rounds of this type of statistical analysis were implemented, each one with a different population group as the reference category. Specifically, the three categories taken as reference were i) those who did not get to enter into primary school; ii) those who completed tertiary school; and iii) those who completed secondary school.

For AIM 3, to estimate the association between EOCU and failure to finish each of the educational milestones beyond primary school: starting but not finishing secondary school, starting tertiary school, and starting but not finishing tertiary school.

Here, three specific at-risk sub-populations were specified, one for failing to achieve each of the educational milestones that are of interest to this study. Thus, for the study of the association between EOCU and finishing secondary school, the specific at-risk group included participants that at least had entered into secondary school (i.e., people who at least had completed a year in

the cross-country standardized category of secondary level of schooling). This sub-population involves people who had started but who had never finished secondary school, those who were still attending this level of schooling at the time of the interview, or those who had achieved any of the subsequent educational levels at the time of the interview, including college and graduate school. The reason for the focus on participants age 18 years or older is that all the WMHS participating countries included individuals aged at least 18 years. South Africa was an exception to this design rule and included people younger than 18 years, but these individuals (n=36) were excluded from analysis in similar conditions across countries. Japan and Israel were also exceptions to the 18-year rule, as they included participants of the minimum age at 20 or 21 years, respectively.

For the assessment of the association between EOCU and entry into tertiary school (which for some countries constitutes college), I specified the at-risk sub-population as participants who at least had finished secondary school, and were 21 years or older. The reason why I constrain the analysis sample for this milestone to people older than 20 years is that people between 18 and 20 years are still in the age most people enter into tertiary school and in that regard, they would not constitute a failure if by that age at interview they still have not achieved that milestone.

Finally, to assess the link between EOCU and failure to finish tertiary school, the at-risk group involved those participants who at least had entered tertiary school and were at least 25 years. Again, this age constraint allows it to leave out people who were too young to expect to have completed tertiary school. Specifically, it can prove to be a mistake to consider people between 18 and 24 as failures if they have not completed this milestone, as they are still in the age most people complete tertiary school. Table 1 conveys the number of people meeting these criteria for the at-risk groups for each of the outcomes of interest.

The analysis plan for Aim 3 then followed a standard three-step approach that includes: i) exploration of the marginals (i.e., Tukey-style Exploratory Data Analysis); ii) analysis/estimation; and iii) post-estimation exploration (e.g., regression diagnostics; subgroup variation assessment). For the estimation of proportions, the complexity of the sampling methods was taken into account through the use of weights that track back the sampling selection probabilities, as well as through post-stratification adjustment factors, and the multi-stage nested structure of the sampling plan implemented in each country.

In general, all analyses were country-specific based on the assumption that environmental circumstances for both drug use and educational attainment might vary appreciably across countries. This might even be true for countries from the same region (e.g., USA and Mexico or Colombia) or level of economic development (e.g., within low-income or middle-income strata).

Thus, in the initial analysis step, there was an estimation of country-specific and pooled cumulative occurrences of EOCU and failure to reach each of the three educational milestones among the corresponding at-risk populations. Firstly, there was an estimation of the occurrence of EOCU and failure to finish secondary school among those who at least got to enter into secondary school (for Japan, the minimum age was 20, and for Israel, it was 21, as these were the age limits for recruitment). Secondly, there was an estimation of the occurrence of EOCU and failure to enter tertiary school among those who at least finished secondary school; and, finally, the occurrence of EOCU and failure to finish tertiary school was estimated among those who got to enter this level of schooling.

Subsequently, a conditional logistic regression is implemented matching individuals by geographical areas of residence to estimate the crude and the adjusted association between EOCU

and failure to achieve each of the three educational milestones beyond entering secondary school, including completing secondary school, entry into tertiary school and completing tertiary school. Given the possibility of variations across countries, separate analyses by country were performed. Two basic levels of adjustment were considered: i) one that includes sex, age, and age squared as covariates; and ii) one that includes childhood traits and experiences that are known to have an effect on both drug involvement and educational attainment. These covariates are as described above in Section 3.6.3.

Given that a knowledgeable audience may take as a limitation that the conditional form of logistic regression does not consider the complexity of the sampling methodology used by the WMHS, crude and adjusted unconditional logistic regression models for complex samples were fitted. With this approach, the consistency of the results using the different analytical methodologies possible to use, given the nature of the data available for this study, can be assessed.

Lastly, a meta-analytic approach was used to achieve a weighted adjusted summary estimate of the EOCU effect on each of the three educational milestones studied using information from all 16 countries. The conditional and unconditional forms of logistic regression analysis produced the country-specific estimates used in the meta-analysis. I based the analyses on conservative random-effect models because I assume that the hypothesized EOCU effect was not common (i.e., homogeneous) across countries and that the variation among countries was not due to random variation only. In other words, I hold the assumption that there is a distribution of EOCU effects on the outcomes given the different contexts of each country (Dohoo, Martin, and Stryhn 2003).

In the post-estimation exploration step, the possibility that the effect of EOCU on completing each of the educational milestones varies for males and females or across age groups was tested. Also, a validity assessment was performed to evaluate if the association estimates that link EOCU and educational milestones were influenced by the fact that there are people who did not give an exact age of onset of cannabis but said it was before the twenties and therefore coded by design as if the age of onset would have been at age 19, and by the fact that there are people who said that they started to use cannabis before age 6. In both cases, the series of analyses were repeated to address these two situations, one in which those who are aged 19 years are dropped and one in which those whose age of onset is before age 6 are dropped.

As for Type I error control, the alpha was set at 0.05, and the odds ratio presented with their respective 95% confidence intervals (95% CI) and p-values under the models used. For cumulative occurrence estimates, the variances for complex samples were estimated via the Taylor series linearization (delta) method. All analyses were completed using Stata software, version 13 (*Stata Statistical Software* (version 13) 2013).

In its Results sections, this dissertation research report follows contemporary recommendations to avoid the use of adjectives such as ‘statistically significant’ and ‘significant’ when estimated p-values are below 0.05. As an alternative, any estimate for which $p<0.05$ is described as ‘robust’ or as ‘precise’ or as ‘robust and precise,’ and these adjectives are meant to convey that information, with none of the implications of ‘clinically significant’ or ‘scientifically significant’ findings. Also, ‘public health significance’ is mentioned in the Discussion and Conclusions sections because this evaluation requires subjective judgments about the findings. This evaluation is not a characteristic of the estimates presented as ‘Results’ of this work.

CHAPTER 4. RESULTS

In this chapter, I arranged the results by aim.

4.1. Aim 1

This aim has two parts (Aim 1a and Aim 1b)

4.1.1. To assess the association between history of any cannabis use with school entry

Before I assess the association between school entry, operationally defined as entering into primary school, and history of any cannabis use, operationally defined by age-of-onset based categories of cannabis use, I present in Table 2 and Table 3 a description of these two variables, by country.

In general, as conveyed in Table 2, a very small percentage (less than 5% for all countries except Lebanon, South Africa, and Nigeria) of people failed to enter primary school. Nigeria had the highest percentage of individuals failing to enter primary school at 16.2%, followed by Lebanon with 7.6% and South Africa with 6.6%. On the other hand, the United States, Germany, Netherlands, and Japan had the smallest prevalence with 0.1 or fewer of people failing to enter into primary school. In all the remaining countries, the prevalence of this adverse life event is between 0.5% (in Italy) and 4.6% (in Mexico).

Table 2. Estimated occurrence of failing to enter into primary school and occurrence of cannabis use by age of onset category. Data from the first 16 participating sites of the World Mental Health Surveys Consortium, 2002-2007

Region/Country	Total of study participants 18+ years old*	History of entering into educational trajectory: Failed to enter primary school n[a] (wt%)[b]	History of cannabis use by age of onset [c]			
			Never users n[a] (wt%)[b]	Onset after age 16 n[a] (wt%)[b]	Onset between age 6 and 16 n[a] (wt%)[b]	Onset before age 6 n[a] (wt%)[b]
Americas						
Colombia	4426	160 (3.5)	4011 (89.2)	265 (7.2)	144 (3.4)	3 (0.2)
Mexico	5782	312 (4.6)	5386 (92.2)	248 (4.9)	128 (2.8)	3 (0.1)
United States	5692	3 (<0.1)	2849 (57.6)	1523 (23.8)	1286 (18.5)	11 (0.1)
Europe						
Belgium	1043	20 (3)	931 (89.6)	73 (7.1)	36 (3.3)	--
France	1436	--	1133 (81)	204 (12.3)	99 (6.7)	--
Germany	1323	3 (0.1)	1069 (82.7)	182 (13)	66 (4.2)	1 (0.1)
Italy	1779	9 (0.5)	1648 (93.5)	92 (4.8)	37 (1.7)	1 (<0.1)
Netherlands	1094	1 (<0.1)	847 (80.2)	175 (12.4)	71 (7.5)	--
Spain	2121	123 (3.3)	1789 (84.1)	216 (10.2)	113 (5.6)	1 (<0.1)
Ukraine	1720	--	1617 (93.7)	69 (4.6)	30 (1.7)	--
Middle East and Africa						
Israel	4859	97 (1.8)	4263 (88.6)	489 (10.1)	59 (1.3)	3 (<0.1)
Lebanon	1031	102 (7.6)	980 (95.4)	46 (4.4)	4 (0.2)	--
Nigeria	2143	473 (16.2)	2056 (97.3)	48 (2)	23 (0.7)	--
South Africa	4351	326 (6.6)	4035 (92.5)	191 (5.2)	67 (2.3)	--
Asia						
Japan	1305	2 (<0.1)	1277 (98.7)	14 (1.2)	--	--
People's Republic of China	1628	43 (3.6)	1612 (99.8)	6 (0.2)	--	--

* These numbers correspond to the denominator to calculate both the occurrence of failing to enter into primary school and the occurrence of cannabis use. As such, these numbers correspond to those 18+ olds who were administered the drug module, which, for most of the countries, corresponded to Part 2 of the survey(except for Mexico, Colombia, Israel, and South Africa, in which the drug module was administered in Part 1 of the survey).

[a] Unweighted count

[b] Weighted estimate

[c] 49 people had missing the age of cannabis use onset, even when they had used cannabis at least once in their life; 30 of them were from South Africa

Also, in Table 2, it can be seen that in general, most people never used cannabis. Thus, this table shows that for most countries, between 80% and 95% of people never have used cannabis. An exception is the United States, where the percentage of never users of cannabis is 57.7%. The same table shows that most of those who have ever used cannabis engaged in that behavior after turning 16 years old. An earlier use of cannabis, i.e., that one that starts between ages 6 and 16,

was found for most of the countries between 0.2 and 7.5% of the general population. Again, the US is an exception. In this country, 18.5% of the population started to use cannabis between ages 6 and 16 years. These results show that in the US, not only do a larger percentage of the population use cannabis, but they also start engaging in this behavior earlier in life in comparison with the other countries.

Table 3 conveys the statistical association between cannabis use and failing to enter school in the crude analysis. An initial association was found in the crude analysis where those who have used cannabis either at an age between 6 and 16 years of age or after age 16 were less likely than those who never used the drug to not enter into the schooling trajectory by age 18. However, after introducing sex and age into the model as covariates, the association was no longer robust or precise ($p>0.05$ and wide confidence intervals). The analysis held constant social-shared factors such as neighborhood-related characteristics via conditional logistic regression.

Table 3. Estimated association between failing to enter into primary school and age of onset-related type of cannabis use, sex, and age

	Data without data imputation			
	Crude		Sex and age-adjusted	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Cannabis use				
Never users	Ref.		Ref.	
Users with onset after age 16	0.3 (0.2, 0.5)	<0.001	0.6 (0.4, 1.0)	0.059
Users with onset by age 16 or earlier	0.2 (0.1, 0.5)	<0.001	0.8 (0.4, 1.6)	0.494
Sex				
Female	Ref.		Ref.	
Male	0.5 (0.5, 0.6)	<0.001	0.5 (0.5, 0.6)	<0.001
Age				
Age	1.1 (1.1, 1.1)	<0.001	1.1 (1.1, 1.2)	<0.001
Age square	0.99 (1.0, 1.0)	<0.001	0.99 (1.0, 1.0)	<0.001

* Derived from conditional logistic regression, using the area from which the individuals were drawn as the matching variable

4.1.2. To estimate the degree to which entry into school might predict the onset of cannabis smoking before age 17

Table 4 summarizes the data highlighting those who were early-onset cannabis users in the population. The distribution of early-onset cannabis use varied across continents. Specifically, it can be seen that in Europe, as a continent, EOCU is relatively common, with prevalence proportions in five of the seven countries ranging from 3.4% in Belgium to 7.5% in the Netherlands, while in the other two countries, Italy and Ukraine, the prevalence proportion of EOCU was 1.7% in both countries. In the Americas, the prevalence proportions were somewhat lower in Spanish speaking countries like Colombia and Mexico, where the prevalence of early-onset cannabis use typically runs between 3% and 4%. In the Middle East and Africa, the prevalence of EOCU was lower, ranging from 0.2% in Lebanon to 2.3 in South Africa. It is noteworthy to note that in Japan and the People´s Republic of China, the event of EOCU was so rare, that the sample size was not large enough to derive a statistical estimation of proportions. Additionally, the US deserves a special mention because close to 20% of the population were EOCU.

Table 4. Distribution of early-onset cannabis use, by country

	Cannabis use	
	EOCU	**Everybody else**
	n[a] (wt%)[b]	**n**[a] (wt%)[b]
Americas		
Colombia	147 (3.6)	4276 (96.4)
Mexico	131 (2.9)	5634 (97.1)
USA	1297 (18.7)	4372 (81.3)
Europe		
Belgium	36 (3.4)	1004 (96.6)
France	99 (6.7)	1337 (93.3)
Germany	67 (4.3)	1251 (95.7)
Italy	38 (1.7)	1740 (98.3)
Netherlands	71 (7.5)	1022 (92.5)
Spain	114 (5.6)	2005 (94.4)
Ukraine	30 (1.7)	1685 (98.3)
Africa and Middle east		
Israel	62 (1.3)	4752 (98.7)
Lebanon	4 (0.2)	1026 (99.8)
Nigeria	23 (0.7)	2104 (99.3)
South Africa	67 (2.3)	4226 (97.7)
Asia		
Japan	0	1291 (100)
People's Republic of China	0	1618 (100)

[a] Unweighted count
[b] Weighted estimate

Table 5 conveys that even though there is an initial association in the crude analysis between EOCU and school entry ($p<0.001$), where those who enter into primary school were more likely to be early cannabis users, this association is lost after adjusting for age and sex ($p=0.367$). There was no effect modification by sex ($p=0.998$). All of these results remained similar after excluding those who started cannabis before age 5 (Table 6).

Table 5. Estimated association between early-onset cannabis use and entering into the school trajectory, sex, and age

	Crude		Sex and age-adjusted	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Education				
At least entered into primary	Ref.		Ref.	
Did not enter into primary	0.2 (0.1, 0.5)	<0.001	0.8 (0.3, 1.5)	0.367
Sex				
Female	Ref.		Ref.	
Male	2.2 (2.0, 2.4)	<0.001	2.3 (2.0, 2.5)	<0.001
Age				
Age	1.1 (1.1, 1.1)	<0.001	1.1 (1.1, 1.3)	<0.001
Age square	0.9 (0.9, 0.9)	<0.001	0.9 (0.9, 0.9)	<0.001

* Derived from conditional logistic regression, using the area from which the individuals were drawn as the matching variable

Table 6. Estimated association between early-onset cannabis use and entering into the school trajectory, sex, and age, excluding those that started to use cannabis before age 6

	Crude		Sex and age-adjusted	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Education				
At least entered into primary	Ref.		Ref.	
Did not enter into primary	0.3 (0.1, 0.5)	<0.001	0.5 (0.3, 1.5)	0.367
Sex				
Female	Ref.		Ref.	
Male	2.2 (2.0, 2.4)	<0.001	2.4 (2.0, 2.5)	<0.001
Age				
Age	1.1 (1.1, 1.1)	<0.001	1.1 (1.1, 1.2)	<0.001
Age square	0.9 (0.9, 0.9)	<0.001	0.9n(0.9, 0.9)	<0.001

* Derived from conditional logistic regression, using the area from which the individuals were drawn as the matching variable

4.2. Aim 2. Association between educational level attained and early-onset cannabis use

Table 7 demonstrates the distribution of levels of schooling by country. The analyses revealed that there are differences in the level of schooling attained that are related to levels of development of the country. In other words, countries that are less developed have more people with a school level in the early stages of schooling at the time they were interviewed, while more-developed countries had more people that have attained later stages of schooling. For example, for Colombia and Mexico, about 16% of the population 18 years or older did not achieve more than some primary schooling, while in the US, that level of schooling was held by less than 3% of the population. Mirroring these percentages, Table 7 shows that more than 80% of the USA population has completed at least high school, while these statistics were less than 50% for Colombia and Mexico.

To estimate the association between EOCU and the level of education attained, I performed three rounds of data analysis, each one with a different level taken as reference. Thus, in Table 8, I present the results when those who did not get to enter into primary school were taken as the reference group. In the crude analysis, there was an association between early-onset cannabis use and the level of schooling attained. Those who reached higher levels of schooling were more likely to be early-onset cannabis users compared to those who never entered into primary school. However, all of these associations were lost when sex and age were included in the model as covariates.

Table 7. Distribution of levels of schooling, by country

	Education level n[a] (wt%)[b]						
	No Education	Some 1°	Complete 1°	Some 2°	Complete 2°	Some 3°	Complete 3°
Americas							
Colombia	160 (3.5)	618 (12.9)	655 (13.9)	1080 (23.9)	948 (21.3)	563 (14.8)	402 (9.7)
Mexico	312 (4.6)	756 (12.8)	1084 (17.6)	1837 (33.0)	750 (13.1)	423 (7.9)	620 (11.1)
USA	3 (<0.01)	102 (2.7)	92 (2.1)	651 (11.8)	1712 (32.5)	1709 (27.6)	1422 (23.2)
Europe							
Belgium	20 (3.0)	20 (2.9)	18 (1.5)	257 (22.9)	273 (23.8)	237 (23.5)	218 (22.3)
France					939 (66.1)	257 (18.4)	240 (15.5)
Germany	3 (0.2)	3 (0.3)	1 (<0.01)	34 (3.1)	1162 (87.2)	76 (6.2)	44 (3.1)
Italy	9 (0.5)	474 (28.8)	300 (17.6)	242 (13.6)	368 (19.8)	162 (8.7)	224 (11.1)
Netherlands	1 (<0.01)	62 (5.3)	90 (7.7)	231 (17.3)	134 (11.1)	252 (26.7)	324 (31.9)
Spain	123 (3.3)	524 (22.5)	334 (16.6)	345 (15.9)	121 (5.3)	362 (19.7)	312 (16.7)
Ukraine		58 (1.9)	151 (7.2)	239 (11.4)	559 (34.6)	436 (27.1)	277 (17.8)
Middle East and Africa							
Israel	97 (1.8)	263 (5.1)	266 (5.3)	442 (9.4)	1728 (36.9)	800 (16.2)	1263 (25.3)
Lebanon	102 (0.7)	180 (16.9)	63 (5.8)	321 (29.6)	114 (12.4)	89 (10.2)	162 (17.6)
Nigeria	473 (16.3)	130 (5.4)	382 (17.2)	522 (25.6)	309 (17.9)	204 (11.1)	123 (6.7)
South Africa	326 (6.6)	624 (13.0)	269 (5.7)	1531 (35.8)	952 (23.2)	503 (12.5)	146 (3.1)
Asia							
Japan	2 (<0.01)	3 (0.3)	28 (2.2)	342 (27.5)	465 (32.7)	265 (20.8)	200 (16.3)
People's Republic of China	43 (3.6)	55 (3.1)	70 (6.0)	626 (32.3)	379 (26.1)	418 (26.8)	37 (2.1)

[a] Unweighted count
[b] Weighted estimate

Table 8. Estimated association between early-onset cannabis use and level of education, sex, and age

	Crude		Sex and age-adjusted	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Education				
Did not enter into 1° school	Ref.		Ref.	
Some 1° school	2.3 (1.0, 5.0)	0.043	1.5 (0.7, 3.5)	0.334
Completed 1° school	3.2 (1.5, 7.0)	0.004	1.5 (0.7, 3.4.0)	0.348
Some 2° school	6.7 (3.1, 14.4)	<0.001	2.0 (0.9, 4.4)	0.093
Completed 2° school	4.5 (2.1, 9.7)	<0.001	1.1 (0.5, 2.4)	0.831
Entered into college	4.8 (2.3, 10.5)	<0.001	1.0 (0.5, 2.3)	0.892
Complete college or more	3.5 (1.6, 7.5)	0.001	0.8 (0.3, 1.7)	0.507
Sex				
Female	Ref.		Ref.	
Male	2.2 (2.0, 2.4)	<0.001	2.3 (2.1, 2.5)	<0.001
Age				
Age	1.1 (1.1, 1.1)	<0.001	1.1 (1.1, 1.2)	<0.001
Age square	0.9 (0.9, 0.9)	<0.001	0.9 (0.9, 0.9)	<0.001

* Derived from conditional logistic regression, using the area from which the individuals were drawn as the matching variable

Table 9 shows that when the reference group is the one that involves those who completed tertiary school, every group that did not make it to that educational milestone was more likely to have started cannabis use before 17 years. When the model was adjusted by age and sex, the statistical association remained except for those who did not enter primary school.

Table 9. Estimated association between early-onset cannabis use and level of education, sex, and age

	Crude*		Sex and age-adjusted	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Education				
Did not enter into 1° school	0.3 (0.1, 0.6)	0.001	1.3 (0.6, 2.9)	0.507
Some 1° school	0.7 (0.5, 0.9)	0.005	2.0 (1.4, 2.7)	<0.001
Completed 1° school	0.9 (0.7, 1.2)	0.533	1.9 (1.5, 2.6)	<0.001
Some 2° school	1.9 (1.6, 2.3)	<0.001	2.6 (2.2, 3.1)	<0.001
Completed 2° school	1.3 (1.1, 1.5)	<0.001	1.4 (1.2, 1.7)	<0.001
Entered into college	1.4 (1.2, 1.6)	<0.001	1.3 (1.2, 1.6)	<0.001
Complete college or more	Ref.		Ref.	

* Derived from conditional logistic regression, using the area from which the individuals were drawn as the matching variable
** Adjusted by sex, age, age-square, conduct problems during childhood or adolescence, hyperactivity and attention problems during childhood, early-onset of cocaine, extramedically used prescription drugs, other illegal drugs use, and eight childhood circumstances (1. having lived with both biological parents up to age sixteen; 2. years of education of mother; 3. years of education of father; 4. having witnessed violence between parents or persons who raised the participant; 5. physical abuse; 6. neglect; 7. having witnessed symptoms compatible with depression, anxiety, mania, drug-related problems or suicide intent in parents or persons who raised the participant).

Table 10 presents the circumstance in which the group that completed secondary school was the reference group, which is the most common circumstance for most countries concerning the highest educational level attained. After adjustment by sex and age, compared to those completing secondary school, those with some primary, have completed primary, or have some secondary school were more likely to have started cannabis use before 17 years. Interestingly, there was no difference between those who did not enter into the schooling trajectory and those who completed secondary. Similarly, those who entered tertiary school did not differ from those who completed secondary school. However, those who completed tertiary school were less likely to have started cannabis before age 17 than those who completed secondary school.

Table 10. Estimated association between early-onset cannabis use and level of education, sex, and age

	Crude*		Sex and age-adjusted	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Education				
Did not enter into 1° school	0.2 (0.1, 0.5)	<0.001	0.9 (0.4, 2.0)	0.831
Some 1° school	0.5 (0.4, 0.7)	<0.001	1.4 (1.0, 1.9)	0.037
Completed 1° school	0.7 (0.6, 0.9)	0.008	1.4 (1.0, 1.8)	0.026
Some 2° school	1.5 (1.3, 1.7)	<0.001	1.8 (1.5, 2.1)	<0.001
Completed 2° school	Ref		Ref	
Entered into college	1.1 (1.0, 1.2)	0.229	1.0 (0.8, 1.1)	0.658
Complete college or more	0.8 (0.7, 0.9)	<0.001	0.7 (0.6, 0.8)	<0.001

* Derived from conditional logistic regression, using the area from which the individuals were drawn as the matching variable
** Adjusted by sex, age, age-square, conduct problems during childhood or adolescence, hyperactivity and attention problems during childhood, early-onset of cocaine, extramedically used prescription drugs, other illegal drugs use, and eight childhood circumstances (1. having lived with both biological parents up to age sixteen; 2. years of education of mother; 3. years of education of father; 4. having witnessed violence between parents or persons who raised the participant; 5. physical abuse; 6. neglect; 7. having witnessed symptoms compatible with depression, anxiety, mania, drug-related problems or suicide intent in parents or persons who raised the participant).

4.3. Aim 3

This aim has three parts focused on exploring the association between early-onset cannabis use and failure to achieve each of the educational milestones beyond primary school, including 1) completing secondary school, 2) entering tertiary school, and 3) completing tertiary school.

4.3.1. EOCU and completing secondary school

In the first part of the third aim, I examine the association between EOCU and finishing secondary school among those who entered secondary school. In this analysis, the sample was restricted to only individuals who entered secondary school. In Table 11, it can be seen that even though the population was restricted, the distribution of early-onset cannabis use resembles the one seen in the general population. Regarding the percentage of people who fail to finish secondary school, the percentage varies widely across countries. For example, while in Mexico and South

Africa only about 50% of individuals who enter into secondary school completed it, in other countries like Germany, Israel and, the US, more than 88% of people who entered secondary school completed it.

Table 11. Estimated occurrence of failing to finish secondary school among people potentially at risk for failing to achieve that educational milestone. Data From the First 16 Participating Sites of the World Mental Health Surveys Consortium, 2002-2007

	People entering into secondary school and are 18 or older		
Region/Country	**Total**	**Failed to finish secondary school**	**EOCU[a]**
		n[b] (wt%)[c]	**n (wt%)**
Americas			
Colombia	2993	1080 (34.2)	107 (3.9)
Mexico	3630	1837 (50.7)	95 (3.3)
United States	5494	651 (12.5)	1274 (19.4)
Europe			
Belgium	985	257 (24.7)	35 (3.6)
France	1436	--	99 (6.7)
Germany	1316	34 (3.1)	67 (4.3)
Italy	996	242 (25.5)	34 (3.1)
Netherlands	941	231 (19.9)	68 (8.4)
Spain	1140	345 (27.6)	96 (8.4)
Ukraine	1510	239 (12.6)	30 (1.9)
Middle East and Africa			
Israel	4,233	442 (10.7)	55 (1.3)
Lebanon	686	321 (42.4)	3 (0.1)
Nigeria	1158	522 (41.8)	17 (0.8)
South Africa	3101	1508 (47.7)	52 (2.6)
Asia			
Japan	1272	342 (28.3)	--
People's Republic of China	1460	626 (37.0)	--

[a] EOCU: Early-onset cannabis use
[b] Unweighted number of people
[c] Estimated cumulative occurrence. Indicates weighted data with Taylor series linearization for variance estimation.

In Table 12, the results of the conditional logistic regression are shown. The analysis revealed a substantial cross-country variation in the association between early-onset cannabis use and failing to complete secondary school once it is started, having as a comparison group everybody else (i.e., those who are never or later-onset cannabis users). Specifically, for countries like Israel and those in the Americas, the association was robust and mostly kept after introducing age and sex and the other eighteen covariates mentioned in the Methods section. In contrast, there was no association between the two variables for most countries in Europe and Africa, or this was lost after adjustment. For countries like France, Germany, Lebanon, South Africa, Japan, and China, there were too few cases of failure to complete secondary school or EOCU. Therefore, it was not possible to derive statistical estimates for these countries.

Figure 9 shows that the pooled estimate derived using the meta-analytic methods was 1.9 (95% CI: 1.3, 2.7).

In the post-explorative analysis, I also fitted a model that assessed if the probability of failing to complete secondary school was higher for those EOCU participants than those later-onset cannabis users (i.e., users who started after age 16). This model took all countries in a collapsed way. Thus, the fully adjusted model found that, compared with the later-onset users, the EOCU people were more likely not to complete secondary school by age 18 (OR=2.3; 95% CI: 1.7, 3.1; p-value=<0.001). This statistical association remained in the stratified analysis separating the USA and the rest of the countries.

Table 12. Estimated association between early-Onset cannabis use and failure to finish secondary school among those who achieved to enter secondary school: Unadjusted and covariate-adjusted conditional logistic regression. Data from the first 16 participating sites of the World Mental Health Surveys Consortium, 2002-2007

	Model 1[a]			Model 2[b]			Model 3		
Region/Country	Est. OR	95% CI	p-value	Est. OR	95% CI	p-value	Est. OR	95% CI	p-value
Americas									
Colombia	2.3	1.5, 3.4	<0.001	2.7	1.8, 4.0	<0.001	3.3	1.5, 7.4	0.003[c]
Mexico	2.5	1.6, 3.9	<0.001	2.6	1.6, 4.1	<0.001	2.5	1.0, 6.2	0.053[c]
United States	2.1	1.7, 2.5	<0.001	2.5	2.0, 3.0	<0.001	1.6	1.2, 2.3	0.005[c]
Europe									
Belgium	0.8	0.4, 0.9	0.675	3.6	1.4, 9.2	0.008	2.8	0.7, 11.9	0.151[d]
France	--	--	--[f]	--	--	--[f]	--	--	--[f]
Germany	--	--	--[f]	--	--	--[f]	--	--	--[f]
Italy	1.0	0.5, 2.3	0.930	1.4	0.6, 3.3	0.409	1.3	0.5, 3.6	0.573[d]
Netherlands	0.5	0.2, 1.0	0.038	1.1	0.5, 2.4	0.852	1.5	0.5, 4.3	0.436[d]
Spain	0.5	0.3, 0.8	0.008	1.0	0.6, 1.8	0.981	0.5	0.2, 1.5	0.229[d]
Ukraine	1.3	0.5, 3.6	0.585	2.2	0.8, 6.4	0.131	2.1	0.4, 12.7	0.399[d]
Middle East and Africa									
Israel	3.5	1.8, 6.9	<0.001	3.6	1.8, 7.0	<0.001	4.7	1.8, 12.6	0.002[e]
Lebanon	2.2	0.2, 26.6	0,522	3.6	0.3, 43,5	0.311	---	---	---[f]
Nigeria	0.7	0.3, 1.9	0.493	0.8	0.3, 2.3	0.711	1.2	0.3, 4.1	0.806[c]
South Africa	1.9	0.6, 1.7	0.931	1.4	0.8, 2.4	0.302	---	---	---[f]
Asia									
Japan	---	---	---[f]	---	---	---[f]	---	---	---[f]
People's Republic of China	---	---	---[f]	---	---	---[f]	---	---	---[f]

Est. OR, Estimated Odds Ratio; CI, Confidence Interval

[a] Crude relative risk estimated via odds ratio under the conditional form of the logistic regression model

[b] See footnote a, but adjusted by sex, age, and age-squared terms are included as covariates.

[c] Adjusted by sex, age, age-square, conduct problems during childhood or adolescence, hyperactivity and attention problems during childhood, early-onset of cocaine, alcohol, tobacco, extramedically used prescription drugs, other illegal drugs use, and eight childhood circumstances (1. having lived with both biological parents up to age sixteen; 2. having been away from home at least six months up to age eighteen; 3. years of education of mother; 4. years of education of father; 5. having witnessed violence between parents or persons who raised the participant; 6. physical abuse; 7. neglect; 8. having witnessed symptoms compatible with depression, anxiety, mania, drug-related problems, or suicide intent in parents or persons who raised the participant).

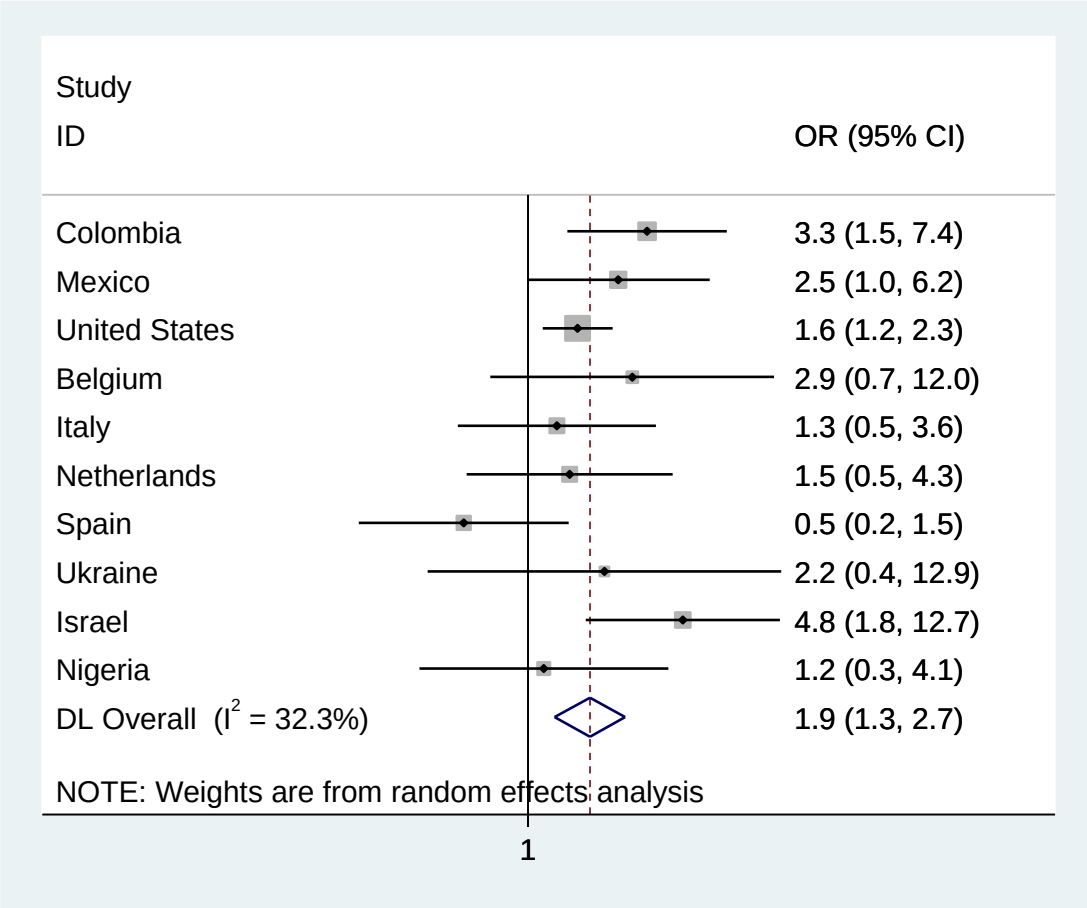
[d] Adjusted by sex, age, age-square, conduct problems during childhood or adolescence, hyperactivity and attention problems during childhood, early-onset of cocaine, alcohol, extramedically used prescription drugs, other illegal drugs, and six childhood circumstances (1. having lived with both biological parents up to age sixteen; 2. having been away from home at least six months up to age eighteen; 3. years of education of mother; 4. years of education of father; 5. having witnessed violence between parents or persons who raised the participant; 6. physical abuse). For Ukraine, the model includes early-onset tobacco use and neglect.

[e] Adjusted by sex, age, age-square, early-onset of cocaine, alcohol, tobacco, extramedically used prescription drugs and other illegal drugs and four childhood circumstances (1. having lived with both biological parents up to age sixteen; 2. having been away from home at least six months up to age eighteen; 3. years of education of mother; 4. years of education of father).

[f] Could not be estimated (too few informative risk sets at these sites, generally due to very low occurrence of early-onset cannabis smoking).

[9] For South Africa, these questions were not asked: 1. having lived with both biological parents up to age sixteen; 2. having been away from home at least six months up to age eighteen; 3. neglect.

Figure 9 Meta-analysis summarizing data derived from the full-adjusted conditional logistic regression: EOCU and failure to finish secondary school



Results from the unconditional logistic regression are seen in Table 13. This table conveys that the patterns of association vary across continents where in the Americas, it can be seen an association between EOCU and failure to complete secondary school that is robust to covariate adjustment (although attenuated for the USA after adjusting for all the eighteen covariates). For countries in the other continents, however, the association is nonexistent except for Israel, where a strong but imprecise association is seen in the crude and fully adjusted model.

Table 13. Estimated association between early-Onset cannabis use and failure to finish secondary school among those who achieved to enter secondary school: Unadjusted and covariate-adjusted. Data from the first 16 participating sites of the World Mental Health Surveys Consortium, 2002-2007

	Model 1[a]			Model 2[b]			Model 3		
Region/Country	Est. OR	95% CI	p-value	Est. OR	95% CI	p-value	Est. OR	95% CI	p-value
Americas									
Colombia	2.0	1.2, 3.3	0.009	2.3	1.4, 3.9	0.002	2.6	1.1, 6.4	0.038 [c]
Mexico	2.5	1.4, 4.7	0.004	2.5	1.4, 4.6	0.004	4.4	1.5, 13.2	0.009 [c]
United States	1.8	1.3, 2.4	0.001	2.0	1.5, 2.7	<0.001	1.6	0.9, 2.7	0.113 [c]
Europe									
Belgium	0.6	0.1, 2.1	0.364	2.7	0.8, 8.7	0.099	2.3	0.3, 17.6	0.404[d]
France	--	--	--[f]	--	--	--[f]	--	--	--[f]
Germany	--	--	--[f]	--	--	--[f]	--	--	--[f]
Italy	1.5	0.5, 4.6	0.434	2.0	0.6, 6.2	0.237	2.1	0.6, 6.7	0.217[d]
Netherlands	0.4	0.2, 1.1	0.069	1.0	0.4, 3.1	0.934	1.2	0.4, 3.8	0.796[d]
Spain	0.8	0.3, 1.8	0.578	1.6	0.6, 4.0	0.337	1.1	0.3, 4.1	0.892[d]
Ukraine	0.6	0.2, 2.5	0.513	1.0	0.2, 4.4	0.996	0.7	0.1, 6.8	0.754[d]
Middle East and Africa									
Israel	3.2	1.6, 6.1	0.001	3.1	1.6, 6.0	0.001	4.9	1.8, 12.9	0.002 [e]
Lebanon	0.6	0.1, 8.5	0.716	0.9	0.1, 10.3	0.915	---	---	--- [f]
Nigeria	0.8	0.3, 2.3	0.672	0.8	0.3, 2.3	0.676	1.2	0.3, 4.4	0.757 [c]
South Africa	0.9	0.5, 1.6	0.619	1.1	0.6, 2.1	0.792	0.2	0.0, 30.4	0.496 [g]
Asia									
Japan	---	---	---[f]	---	---	---[f]	---	---	---[f]
People's Republic of China	---	---	---[f]	---	---	---[f]	---	---	---[f]

Est. OR, Estimated Odds Ratio; CI, Confidence Interval

[a] Crude relative risk estimated via odds ratio under the unconditional form of the logistic regression model

[b] See footnote a, but adjusted by sex, age, and age-squared terms are included as covariates.

[c] Adjusted by sex, age, age-square, conduct problems during childhood or adolescence, hyperactivity and attention problems during childhood, early-onset of cocaine, alcohol, tobacco, extramedically used prescription drugs, other illegal drugs use, and eight childhood circumstances (1. having lived with both biological parents up to age sixteen; 2. having been away from home at least six months up to age eighteen; 3. years of education of mother; 4. years of education of father; 5. having witnessed violence between parents or persons who raised the participant; 6. physical abuse; 7. neglect; 8. having witnessed symptoms compatible with depression, anxiety, mania, drug-related problems, or suicide intent in parents or persons who raised the participant).

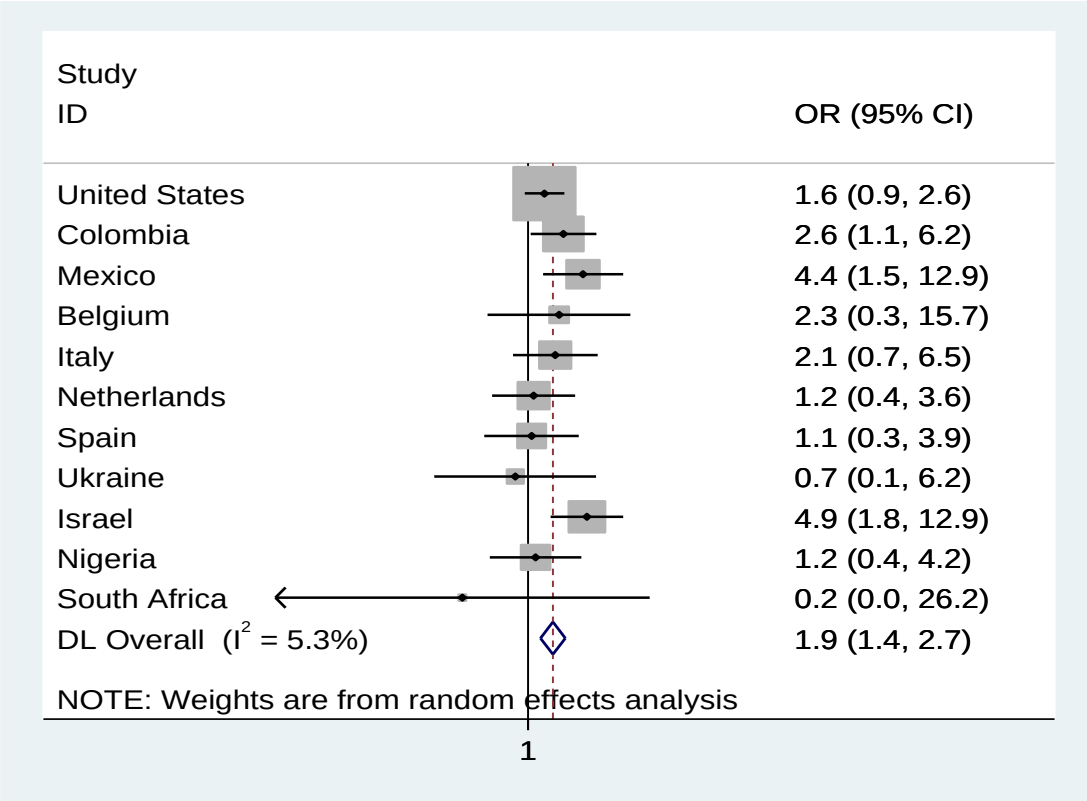
[d] Adjusted by sex, age, age-square, conduct problems during childhood or adolescence, hyperactivity and attention problems during childhood, early-onset of cocaine, alcohol, extramedically used prescription drugs, other illegal drugs, and six childhood circumstances (1. having lived with both biological parents up to age sixteen; 2. having been away from home at least six months up to age eighteen; 3. years of education of mother; 4. years of education of father; 5. having witnessed violence between parents or persons who raised the participant; 6. physical abuse). For Ukraine, the model includes early-onset tobacco use and neglect.

[e] Adjusted by sex, age, age-square, early-onset of cocaine, alcohol, tobacco, extramedically used prescription drugs and other illegal drugs and four childhood circumstances (1. having lived with both biological parents up to age sixteen; 2. having been away from home at least six months up to age eighteen; 3. years of education of mother; 4. years of education of father).

[f] Could not be estimated (too few informative risk sets at these sites, generally due to very low occurrence of early-onset cannabis smoking).
[g] For South Africa, these questions were not asked: 1. having lived with both biological parents up to age sixteen; 2. having been away from home at least six months up to age eighteen; 3. neglect.

A meta-analysis was performed using the full-adjusted unconditional logistic regression model results to summarize data from the sixteen countries. Figure 10 shows a pooled estimate of 1.9 (95% CI: 1.4, 2.7).

Figure 10 Meta-analysis summarizing data derived from the full-adjusted unconditional logistic regression: EOCU and failure to finish secondary school



Pooled estimate with random treatment: Odds Ratio: 1.9 (95% CI: 1.4, 2.7)

In summary, this study found consistent evidence that the EOCU is associated with failing to complete secondary school once it is begun.

4.3.2. Early-onset cannabis use and entering college

To examine the association between EOCU and failure to enter into tertiary school, the analysis was restricted to the population of 21-year-olds or older who had completed secondary school. Table 14 shows that there is a wide variability across countries in the percentage of this type of population who failed to enter the tertiary school once they completed secondary school. For example, within Europe, Spain, and the Netherlands, an estimated percentage of 13.2% and 17.3% of those who completed secondary school but failed to continue to tertiary school. These percentages are in contrast with those of countries such as Germany and France, where 90% and 66% of the population who completed secondary school failed to enter college. In the Americas, the percentage of those failing to enter tertiary school has a narrower range, going from 37.7% in the USA to 45.8% in Colombia; the same narrow range is seen in Asia, with a percentage of 43.2% in China and 47.1% in Japan. In the Middle East and Africa, the range is from 28.9% in Lebanon to 56.6% in South Africa.

Table 14 also conveys the percentage of EOCU among those who are 21 or older and completed secondary school. These percentages reflect the estimates for the lifetime history of ever using cannabis, with the USA leading by far with 17.4%, followed by the Netherlands (9.5%), Spain (7.8%) and France (5.5%). The rest of the participant countries had prevalence proportions of EOCU under 5%, while in both countries in Asia it was difficult to estimate stable coefficients as the event was very rare.

Table 14. Estimated occurrence of failing to enter into college among people potentially at risk for failing to achieve that educational milestone. Data From the First 16 Participating Sites of the World Mental Health Surveys Consortium, 2002-2007

Region/Country	People finishing secondary school and are 21 or older		
	Total	Failed to enter college	EOCU[a]
		n[b] (wt%)[c]	n (wt%)
Americas			
Colombia	1692	826 (45.8)	37 (2.3)
Mexico	1581	644 (39.5)	23 (1.9)
United States	4581	1569 (37.7)	959 (17.4)
Europe			
Belgium	701	265 (34.6)	22 (3.0)
France	1383	909 (66.7)	83(5.5)
Germany	1266	1148 (90.7)	63 (4.2)
Italy	717	351 (49.8)	24 (2.8)
Netherlands	689	131 (17.3)	54 (9.5)
Spain	749	113 (13.2)	64 (7.8)
Ukraine	1204	517 (42.3)	16 (1.4)
Middle East and Africa			
Israel	3791	1728 (47.1)	42 (1.1)
Lebanon	330	101 (28.9)	1 (0.2)
Nigeria	562	249 (44.3)	11 (1.0)
South Africa	1413	799 (56.6)	25 (2.9)
Asia			
Japan	924	463 (47.1)	--
People's Republic of China	753	337 (43.2)	--

[a] EOCU: Early-onset cannabis use
[b] Unweighted number of people
[c] Estimated cumulative occurrence. Indicates weighted data with Taylor series linearization for variance estimation.

Table 15 shows us the results of the conditional logistic regression. In the initial crude examination, no robust or precise relationships were found between early-onset cannabis use and entering college for most countries. The USA and three European countries were exceptions (i.e., France, Germany, and the Netherlands). In the case of these three European countries, an initial inverse association between the two variables was lost after covariate adjustment. However, for the USA, the initial positive association seen in the crude model remained even after the adjustment with the eighteen covariables. Finally, this table also conveys that sample size restrictions did not allow to derive estimates for Lebanon, Japan, and China. Similarly, for South Africa, the full-adjustment model did not converge, given the small number of cases.

The meta-analysis (Figure 11) with data derived from each country's conditional logistic regression models yielded a summary estimate of 1.4 (95% CI: 1.1, 1.7).

Also, in the post-explorative analysis, a model assessed the possibility that failing to enter tertiary school was higher for those EOCU participants than those later-onset cannabis users (i.e., users who started after age 16). This model took all countries in a collapsed way, as well. Thus, the fully adjusted model found that, compared with the later-onset users, the EOCU people were more likely not to complete secondary school by age 18 (OR=1.6; 95% CI: 1.2, 2.0; p-value=<0.001). This statistical association remained in the stratified analysis separating the USA and the rest of the countries.

Table 15. Estimated association between early-onset cannabis use and failure to enter into tertiary school among those who achieved to enter to complete secondary school: Unadjusted and covariate-adjusted conditional logistic regression. Data from the first 16 participating sites of the World Mental Health Surveys Consortium, 2002-2007

	Model 1[a]			Model 2[b]			Model 3		
Region/Country	Est. OR	95% CI	p-value	Est. OR	95% CI	p-value	Est. OR	95% CI	p-value
Americas									
Colombia	1.0	0.5, 2.0	0.894	1.1	0.5, 2.1	0.880	1.1	0.3, 3.8	0.921 [c]
Mexico	1.8	0.8, 4.1	0.179	2.0	0.9, 4.7	0.102	2.0	0.3, 12.8	0.472 [c]
United States	1.3	1.1, 1.5	<0.001	1.6	1.3, 1.8	<0.001	1.5	1.2, 1.9	0.001 [c]
Europe									
Belgium	0.8	0.3, 2.1	0.645	1.0	0.4, 2.8	0.952	2.5	0.6, 11.0	0.215 [d]
France	0.4	0.2, 0.6	<0.001	0.9	0.5, 1.5	0.638	1.1	0.5, 2.1	0.863 [d]
Germany	0.3	0.2, 0.6	0.001	0.9	0.2, 1.0	0.044	1.1	0.4, 3.1	0.890 [d]
Italy	0.5	0.2, 1.2	0.127	0.5	0.2, 1.2	0.119	0.5	0.2, 1.3	0.136 [d]
Netherlands	0.2	0.1, 0.8	0.021	0.4	0.1, 1.4	0.115	0.3	<0.1, 2.3	0.239 [d]
Spain	0.8	0.4, 1.8	0.631	1.2	0.5, 2.9	0.635	0.6	0.1, 3.0	0.535 [d]
Ukraine	1.9	0.7, 5.4	0.219	1.7	0.6, 5.0	0.319	1.7	0.5, 6.2	0.441[d]
Middle East and Africa									
Israel	1.3	0.7, 2.6	0.405	1.3	0.7, 2.9	0.468	1.8	0.7, 4.9	0.226 [e]
Lebanon	---	---	---[f]	---	---	---[f]	---	---	--- [f]
Nigeria	1.3	0.4, 4.5	0.702	2.1	0.6, 8.0	0.261	2.8	0.4, 17.9	0.282 [c]
South Africa	0.7	0.3, 1.6	0.361	0.6	0.2, 1.4	0.222	---	---	---[f]
Asia									
Japan	---	---	---[f]	---	---	---[f]	---	---	---[f]
People's Republic of China	---	---	---[f]	---	---	---[f]	---	---	---[f]

Est. OR, Estimated Odds Ratio; CI, Confidence Interval

[a] Crude relative risk estimated via odds ratio under the conditional form of the logistic regression model

[b] See footnote a, but adjusted by sex, age, and age-squared terms are included as covariates.

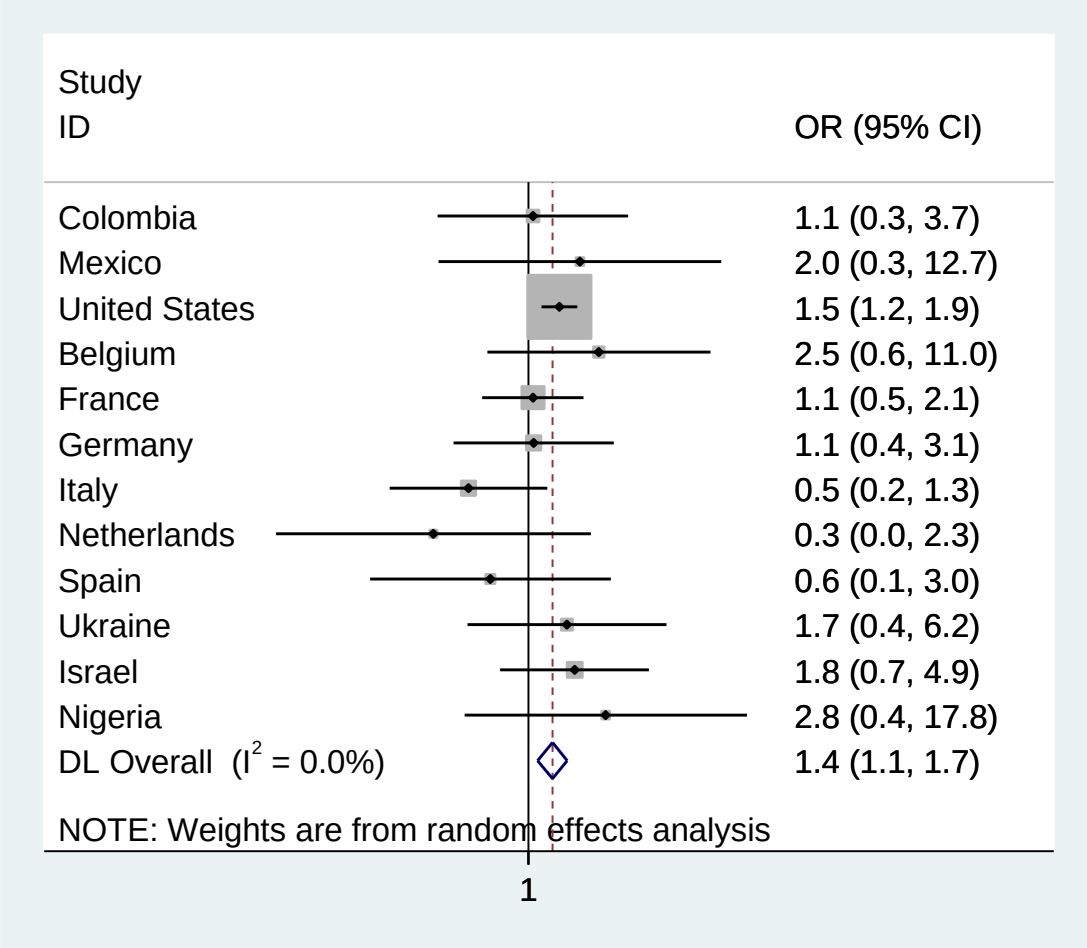
[c] Adjusted by sex, age, age-square, conduct problems during childhood or adolescence, hyperactivity and attention problems during childhood, early-onset of cocaine, alcohol, tobacco, extramedically used prescription drugs, other illegal drugs use, and eight childhood circumstances (1. having lived with both biological parents up to age sixteen; 2. having been away from home at least six months up to age eighteen; 3. years of education of mother; 4. years of education of father; 5. having witnessed violence between parents or persons who raised the participant; 6. physical abuse; 7. neglect; 8. having witnessed symptoms compatible with depression, anxiety, mania, drug-related problems, or suicide intent in parents or persons who raised the participant).

[d] Adjusted by sex, age, age-square, conduct problems during childhood or adolescence, hyperactivity and attention problems during childhood, early-onset of cocaine, alcohol, extramedically used prescription drugs, other illegal drugs, and six childhood circumstances (1. having lived with both biological parents up to age sixteen; 2. having been away from home at least six months up to age eighteen; 3. years of education of mother; 4. years of education of father; 5. having witnessed violence between parents or persons who raised the participant; 6. physical abuse). For Ukraine, the model includes early-onset tobacco use and neglect.

[e] Adjusted by sex, age, age-square, early-onset of cocaine, alcohol, tobacco, extramedically used prescription drugs and other illegal drugs and four childhood circumstances (1. having lived with both biological parents up to age sixteen; 2. having been away from home at least six months up to age eighteen; 3. years of education of mother; 4. years of education of father).

[f] Could not be estimated (too few informative risk sets at these sites, generally due to very low occurrence of early-onset cannabis smoking).
[g] For South Africa, these questions were not asked: 1. having lived with both biological parents up to age sixteen; 2. having been away from home at least six months up to age eighteen; 3. neglect.

Figure 11 Meta-analysis summarizing data derived from the full-adjusted conditional logistic regression: EOCU and failure to enter to tertiary school



In Table 16, country-level data are presented using an unconditional logistic regression model for complex samples. It shows that most of the initial robust or precise associations seen in European Countries in the crude model become non-robust or precise when adjusted for the 18 covariates. In contrast, in the US and Ukraine, the crude analysis did not find an association, but the adjusted model detected robust differences, meaning that those who were EOCU were more likely to fail to enter tertiary school once they completed secondary school. However, the association proved to be marginal for the USA (i.e., p-value very close to the 0.05 limit) and imprecise for Ukraine (i.e., it had a wide 95% confidence interval). In the meta-analysis (Figure 12), the pooled estimate is non-robust or precise with an odds ratio of 1.2 (95% CI: 0.8, 1.8).

In summary, I found evidence suggesting an association between EOCU and failing to enter the tertiary school once secondary school is completed. Specifically, meta-analysis summarizing data derived from each country's conditional logistic regression models found a robust and precise association between the two variables. However, this association seems to be highly influenced by the USA, which may explain the inconsistency found when the estimate lost its robustness when using the unconditional logistic regression results for the meta-analysis.

Table 16. Estimated Association between early-onset cannabis smoking and failure enter to college among those who achieved to finish secondary school: Unadjusted and covariate-adjusted. Data from the first 17 participating sites of the World Mental Health Surveys Consortium, 2002-2007

Region/Country	Model 1[a]			Model 2[b]			Model 3		
	Est. OR	95% CI	p-value	Est. OR	95% CI	p-value	Est. OR	95% CI	p-value
Americas									
Colombia	1.4	06, 3.3	0.452	1.4	0.6, 3.3	0.406	1.5	0.5, 4.3	0.419[c]
Mexico	0.6	0.2, 1.9	0.391	0.7	0.2, 2.0	0.506	1.3	0.3, 7.0	0.735[c]
United States	1.0	0.8, 1.3	0.793	1.3	1.0, 1.6	0.045	1.4	1.0, 1.9	0.049[c]
Europe									
Belgium	0.7	0.2, 2.5	0.550	1.0	0.3, 4.2	0.954	1.1	0.2, 5.6	0.906[d]
France	0.3	0.1, 0.7	0.004	0.7	0.3, 1.6	0.377	0.8	0.3, 2.1	0.600[d]
Germany	0.3	0.1, 0.8	0.015	0.5	0.2, 1.5	0.224	1.9	0.3, 11.6	0.467[d]
Italy	0.3	0.1, 0.9	0.039	0.3	0.1, 0.9	0.036	0.3	0.1, 1.1	0.066[d]
Netherlands	0.1	0.0, 0.4	0.003	0.2	0.1, 0.9	0.041	0.2	0.0, 2.0	0.180[d]
Spain	1.1	0.4, 3.2	0.901	1.2	0.4, 3.8	0.764	1.4	0.3, 7.0	0.681[d]
Ukraine	4.4	1.0, 19.4	0.052	3.5	0.7, 16.2	0.112	9.3	1.7, 55.5	0.012[c]
Middle East and Africa									
Israel	1.5	0.8, 2.8	0.219	1.2	0.6, 2.3	0.613	1.7	0.6, 4.6	0.274[e]
Lebanon[f]	--	--	--	--	--	--	--	--	--[f]
Nigeria	0.6	0.2, 2.3	0.485	1.4	0.4, 4.8	0.573	0.8	0.0,31.6	0.906
South Africa	0.6	0.3, 1.3	0.189	0.5	0.2, 1.4	0.205	1.2	0.3, 5.9	0.792[g]
Asia									
Japan	--	--	--[f]	--	--	--[f]	--	--	--[f]
People's Republic of China	--	--	--[f]	--	--	--[f]	--	--	--[f]

Est. OR, Estimated Odds Ratio; CI, Confidence Interval

[a] Crude relative risk estimated via odds ratio under the unconditional form of the logistic regression model

[b] See footnote a, but adjusted by sex, age, and age-squared terms are included as covariates.

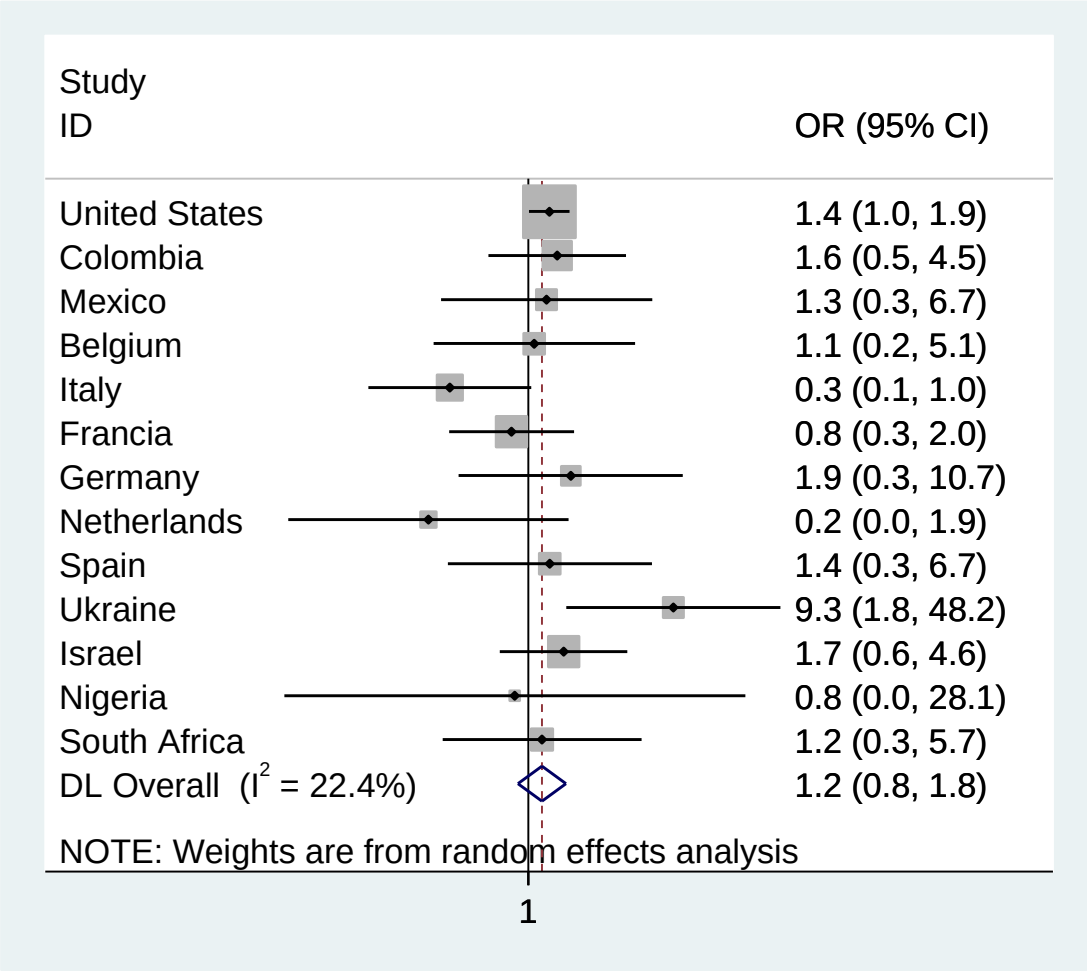
[c] Adjusted by sex, age, age-square, conduct problems during childhood or adolescence, hyperactivity and attention problems during childhood, early-onset of cocaine, alcohol, tobacco, extramedically used prescription drugs, other illegal drugs use, and eight childhood circumstances (1. having lived with both biological parents up to age sixteen; 2. having been away from home at least six months up to age eighteen; 3. years of education of mother; 4. years of education of father; 5. having witnessed violence between parents or persons who raised the participant; 6. physical abuse; 7. neglect; 8. having witnessed symptoms compatible with depression, anxiety, mania, drug-related problems, or suicide intent in parents or persons who raised the participant).

[d] Adjusted by sex, age, age-square, conduct problems during childhood or adolescence, hyperactivity and attention problems during childhood, early-onset of cocaine, alcohol, extramedically used prescription drugs, other illegal drugs, and six childhood circumstances (1. having lived with both biological parents up to age sixteen; 2. having been away from home at least six months up to age eighteen; 3. years of education of mother; 4. years of education of father; 5. having witnessed violence between parents or persons who raised the participant; 6. physical abuse). For Ukraine, the model includes early-onset tobacco use and neglect.

[e] Adjusted by sex, age, age-square, early-onset of cocaine, alcohol, tobacco, extramedically used prescription drugs and other illegal drugs and four childhood circumstances (1. having lived with both biological parents up to age sixteen; 2. having been away from home at least six months up to age eighteen; 3. years of education of mother; 4. years of education of father).

[f] Could not be estimated (too few informative risk sets at these sites, generally due to very low occurrence of early-onset cannabis smoking).
g. For South Africa, these questions were not asked: 1. having lived with both biological parents up to age sixteen; 2. having been away from home at least six months up to age eighteen; 3. neglect.

Figure 12 Meta-analysis summarizing data derived from the full-adjusted unconditional logistic regression: EOCU and failure to enter to tertiary school



Pooled estimate with random treatment: 1.2 (95% CI: 0.8, 1.8)

4.3.3. Early-onset cannabis use and finishing college among those who entered and are 25 years of age or older

Table 17 estimates the occurrence of failing to finish college among people potentially at risk for failing to achieve that educational milestone. Results show that for most countries, more than 50% of those who enter into tertiary school fail to complete it. The exceptions are Mexico, Italy, Netherlands, Israel, and Lebanon, where these proportions are less than 40%. The distribution of early-onset use in this subpopulation of individuals who at least enter into tertiary school is somewhat similar to the general population.

The conditional logistic regression results are presented in Table 18, which conveys that the association in the crude model was null for most of the countries, except for Spain and the USA. After adjusting by the 18 covariates, the association was kept only for the USA. The sample size was insufficient for Ukraine, Lebanon, Japan, and China, which imposed restrictions that did not allow any statistical modeling. For Mexico, Germany, Nigeria, and South Africa, sample size allowed for crude and age-and-sex adjusted modeling but not full-adjusted statistical modeling.

The pooled estimate derived from meta-analyzing data from eight counties' conditional logistic regression models did not reach the statistical threshold to reject the null hypothesis. Thus, the pooled odds ratio was 1.3 (95% CI: 1.0, 1.6).

Additionally, as was the case for the previous educational milestones, and using the same statistical approach, EOCU people were more likely than later-onset cannabis users of failing to complete tertiary school once it started (OR: 1.5; 95% CI: 1.1, 2.1).

Country-level data are presented in Table 19, where the crude model yielded robust or precise associations for Colombia, the US, and Spain, although these associations are lost after adjusting for the full set of covariates. The meta-analysis methods could be applied only for four countries (Figure 14), and the full estimate was not robust or precise with an odds ratio of 1.2 (95% CI: 0.7, 2.0).

Table 17. Estimated occurrence of failing to finish college among people potentially at risk for failing to achieve that educational milestone. Data From the First 16 Participating Sites of the World Mental Health Surveys Consortium, 2002-2007

Region/Country	People entering college and are 25 or older		
	Total	Failed to finish college	EOCU[a]
		n[b] (wt%)[c]	n (wt%)
Americas			
Colombia	729	369 (51.1)	17 (2.0)
Mexico	783	241 (29.8)	9 (2.5)
United States	2743	1416 (50.9)	510 (16.3)
Europe			
Belgium	411	209 (48.7)	10 (2.0)
France	428	217 (51.8)	36 (7.8)
Germany	101	62 (65.7)	7 (1.9)
Italy	326	115 (35.0)	14 (4.4)
Netherlands	534	228 (42.9)	45 (9.0)
Spain	560	300 (52.3)	43 (6.9)
Ukraine	646	383 (57.4)	3 (0.3)
Middle East and Africa			
Israel	1980	747 (37.7)	16 (0.8)
Lebanon	187	51 (27.6)	1 (0.4)
Nigeria	279	164 (55.8)	5 (1.4)
South Africa	516	393 (78.9)	7 (3.1)
Asia			
Japan	418	229 (53.3)	--
People's Republic of China	359	322 (89.6)	--

[a] EOCU: Early-onset cannabis use
[b] Unweighted number of people
[c] Estimated cumulative occurrence. Indicates weighted data with Taylor series linearization for variance estimation.

Table 18. Estimated association between early-Onset cannabis use and failure to complete tertiary school among those who achieved to enter into that level of schooling: Unadjusted and covariate-adjusted conditional logistic regression. Data from the first 16 participating sites of the World Mental Health Surveys Consortium, 2002-2007.

	Model 1[a]			Model 2[b]			Model 3		
Region/Country	Est. OR	95% CI	p-value	Est. OR	95% CI	p-value	Est. OR	95% CI	p-value
Americas									
Colombia	1,7	0.6, 4.9	0.319	2.2	0.7, 6.3	0.155	0.9	0.2, 5.2	0.895 [c]
Mexico	3.8	0.9, 16.3	0.078	5.2	1.2, 23.1	0.031	--	--	-- [f]
United States	1.4	1.2, 1.8	<0.001	1.5	1.2, 1.9	<0.001	1.4	1.1, 1.9	0.017 [c]
Europe									
Belgium	0.6	0.2, 2.4	0.492	0.6	0.2, 2.4	0.472	0.5	0.1, 3.3	0.482 [d]
France	1.1	0.5, 2.2	0.785	1.3	0.6, 2.7	0.511	1.0	0.4, 3.1	0.935 [d]
Germany	0.6	0.1, 3.1	0.515	0.8	0.1, 4.4	0.761	--	--	-- [f]
Italy	1.6	0.5, 5.2	0.461	2.1	0.6, 7.2	0.261	2.4	0.6, 9.7	0.219 [d]
Netherlands	0.8	0.4, 1.5	0.436	0.9	0.4, 1.7	0.704	1.1	0.4, 2.5	0.895 [d]
Spain	0.5	0.2, 1.0	0.040	0.6	0.3, 1.3	0.188	0.7	0.3, 1.8	0.447 [d]
Ukraine	--	--	-- [f]	--	--	-- [f]	--	--	-- [f]
Middle East and Africa									
Israel	0.6	0.2, 1.7	0.303	0.6	0.2, 1.7	0.289	0.6	0.1, 3.1	0.499 [e]
Lebanon	--	--	-- [f]	--	--	-- [f]	---	---	--- [f]
Nigeria	2.9	0.3, 27.0	0.346	4.2	0.4, 40.9	0.212	---	---	--- [f]
South Africa	0.6	0.1, 4.2	0.629	0.6	0.1, 3.7	0.542	---	---	--- [f]
Asia									
Japan	---	---	---[f]	---	---	---[f]	---	---	---[f]
People's Republic of China	---	---	---[f]	---	---	---[f]	---	---	---[f]

Est. OR, Estimated Odds Ratio; CI, Confidence Interval

[a] Crude relative risk estimated via odds ratio under the conditional form of the logistic regression model

[b] See footnote a, but adjusted by sex, age, and age-squared terms are included as covariates.

[c] Adjusted by sex, age, age-square, conduct problems during childhood or adolescence, hyperactivity and attention problems during childhood, early-onset of cocaine, alcohol, tobacco, extramedically used prescription drugs, other illegal drugs use, and eight childhood circumstances (1. having lived with both biological parents up to age sixteen; 2. having been away from home at least six months up to age eighteen; 3. years of education of mother; 4. years of education of father; 5. having witnessed violence between parents or persons who raised the participant; 6. physical abuse; 7. neglect; 8. having witnessed symptoms compatible with depression, anxiety, mania, drug-related problems, or suicide intent in parents or persons who raised the participant).

[d] Adjusted by sex, age, age-square, conduct problems during childhood or adolescence, hyperactivity and attention problems during childhood, early-onset of cocaine, alcohol, extramedically used prescription drugs, other illegal drugs, and six childhood circumstances (1. having lived with both biological parents up to age sixteen; 2. having been away from home at least six months up to age eighteen; 3. years of education of mother; 4. years of education of father; 5. having witnessed violence between parents or persons who raised the participant; 6. physical abuse). For Ukraine, the model includes early-onset tobacco use and neglect.

[e] Adjusted by sex, age, age-square, early-onset of cocaine, alcohol, tobacco, extramedically used prescription drugs and other illegal drugs and four childhood circumstances (1. having lived with both biological parents up to age sixteen; 2. having been away from home at least six months up to age eighteen; 3. years of education of mother; 4. years of education of father).

[f] Could not be estimated (too few informative risk sets at these sites, generally due to very low occurrence of early-onset cannabis smoking).
[g] For South Africa, these questions were not asked: 1. having lived with both biological parents up to age sixteen; 2. having been away from home at least six months up to age eighteen; 3. neglect.

Figure 13 Meta-analysis summarizing data derived from the full-adjusted conditional logistic regression: EOCU and failure to complete tertiary school

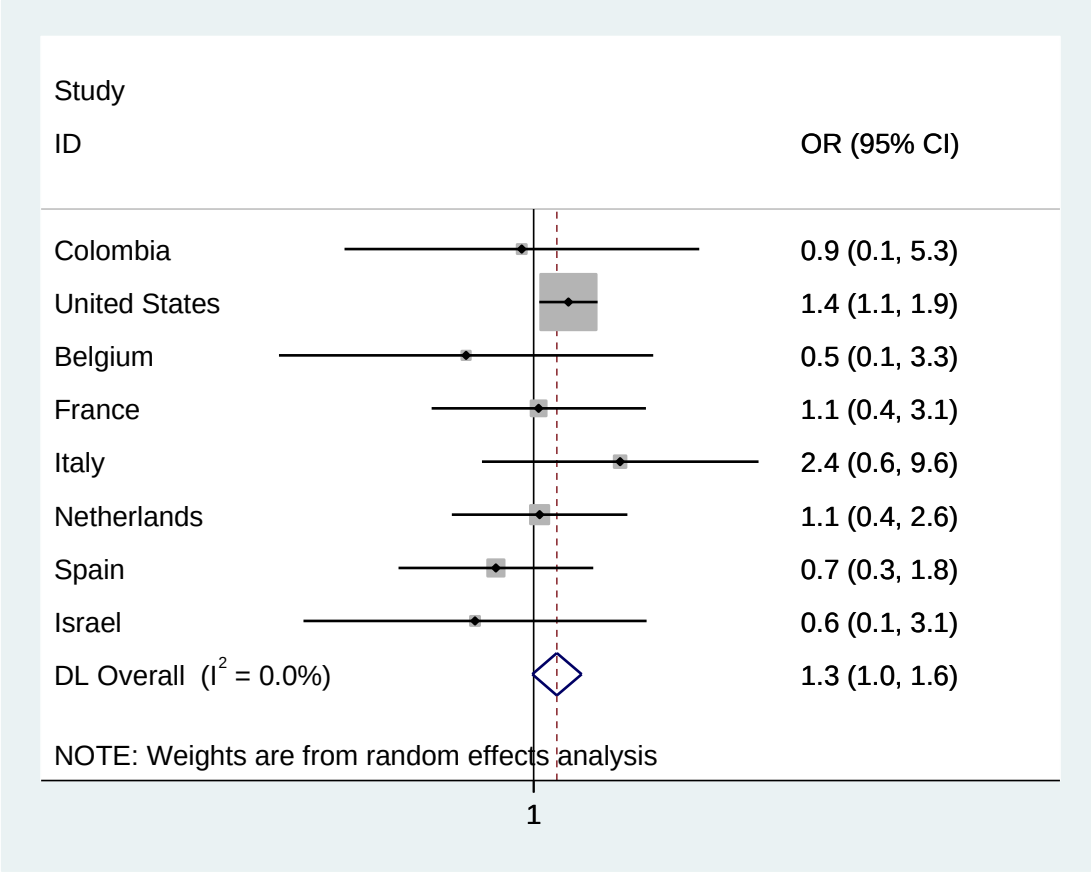


Table 19. Estimated Association between Early-Onset Cannabis Smoking and failure to finish college school among those who achieved to enter to college: Unadjusted and Covariate Adjusted. Data From the First 17 Participating Sites of the World Mental Health Surveys Consortium, 2002-2007.

	Model 1[a]			Model 2[b]			Model 3		
Region/Country	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Americas									
Colombia	3.8	1.4, 10.3	0.009	4.6	1.5, 14.6	0.010	12.2	1.5, 97.3	0.019 [c]
Mexico	6.0	0.9, 41.0	0.069	7.6	1.0, 56.8	0.048	3.6	0.2, 72.6	0.398 [c]
USA	1.4	1.0, 1.9	0.025	1.5	1.1, 2.0	0.020	1.4	1.0, 2.2	0.088 [c]
Europe									
Belgium	0.9	0.1, 5.3	0.898	1.1	0.1, 9.8	0.905	0.3	<0.1, 2.9	0.269 [d]
France	1.8	0.5, 6.2	0.310	2.2	0.6, 8.8	0.240	1.0	0.2, 5.0	0.956[d]
Germany	0.6	0.1, 4.3	0.600	0.5	0.1, 4.1	0.545	--	--	--[f]
Italy	1.5	0.6, 3.9	0.345	1.8	0.6, 5.7	0.285	2.4	0.6, 10.4	0.227 [d]
Netherlands	0.9	0.3, 2.3	0.779	1.2	0.4, 3.0	0.765	0.8	0.3, 2.5	0.743 [d]
Spain	0.4	0.2, 0.9	0.033	0.4	0.2, 1.0	0.040	0.6	0.2, 1.7	0.329
Ukraine	--	--	--[f]	--	--	--[f]	--	--	--[f]
Middle East and Africa									
Israel	0.8	0.3, 2.4	0.683	0.7	0.2, 2.3	0.610	0.6	0.1, 3.7	0.856 [e]
Lebanon	--	--	--[f]	--	--	--[f]	--	--	--[f]
Nigeria	2.4	0.2, 28.3	0.474	3.0	0.3, 34.6	0.372	--	--	--[f]
South Africa	1.1	0.2, 6.6	0.880	1.1	0.1, 9.2	0.929	--[f]	--	--[f]
Asia									
Japan	--	--	--[f]	--	--	--	--[f]	--	--[f]
People's Republic of China[f]	--	--	--[f]	--	--	--	--	--	--[f]

OR, Estimated Odds Ratio; CI, Confidence Interval

[a] Crude relative risk estimated via odds ratio under the unconditional form of the logistic regression model

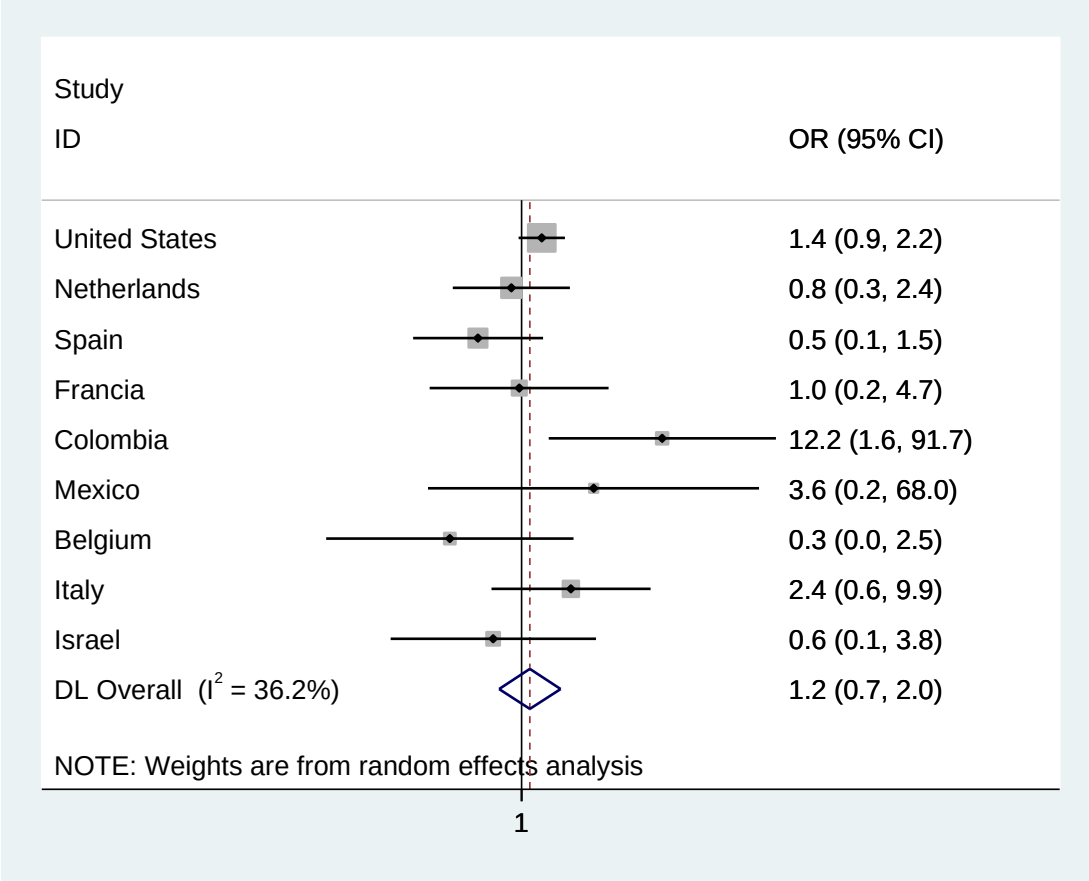
[b] See footnote a, but adjusted by sex, age, and age-squared terms are included as covariates.

[c] Adjusted by sex, age, age-square, conduct problems during childhood or adolescence, hyperactivity and attention problems during childhood, early-onset of cocaine, alcohol, tobacco, extramedically used prescription drugs, other illegal drugs use, and eight childhood circumstances (1. having lived with both biological parents up to age sixteen; 2. having been away from home at least six months up to age eighteen; 3. years of education of mother; 4. years of education of father; 5. having witnessed violence between parents or persons who raised the participant; 6. physical abuse; 7. neglect; 8. having witnessed symptoms compatible with depression, anxiety, mania, drug-related problems, or suicide intent in parents or persons who raised the participant).

[d] Adjusted by sex, age, age-square, early-onset of cocaine **or** extramedically used prescription drugs **or** other illegal drugs, and seven childhood circumstances (1. having lived with both biological parents up to age sixteen; 2. having been away from home at least six months up to age eighteen; 3. years of education of mother; 4. years of education of father; 5. having witnessed violence between parents or persons who raised the participant; 6. physical abuse; 7. neglect).

[e] Adjusted by sex, age, age-square, early-onset of cocaine, extramedically used prescription drugs and other illegal drugs and two childhood circumstances (1. years of education of mother; 2. years of education of father).

Figure 14 Meta-analysis summarizing data derived from the full-adjusted unconditional logistic regression: EOCU and failure to complete tertiary school



Pooled estimate with random treatment: 1.2 (95% CI: 0.7, 2.0)

In summary, this study found consistent evidence that the EOCU is not associated with failing to complete tertiary school once it is begun.

CHAPTER 5. DISCUSSION

This study's main findings can be presented in two stages. The first stage, which addresses aim one and aim two, is meant to set up a context in which results of aim three can be better interpreted. In this stage, I found that there is no association between history of any cannabis smoking and school entry and that there is no association between failure to enter primary school and early-onset cannabis use. Similarly, I found that there is no association between schooling attainment and early-onset cannabis use.

The second stage of findings involves the results for the three sub-aims of aim 3, which underscore key associations that this dissertation is intended to explore. Stage 2 of results indicated that those with early-onset cannabis use were more likely to not complete secondary school among those who entered secondary school (aim 3a). Additionally, I found an association (albeit inconsistent) between early-onset cannabis use and failure to a) enter tertiary school among secondary school completers (aim 3b), and b) complete tertiary school once begun (aim 3c).

The results of aim 1 and aim 2 can be interpreted as an exploration of selection bias that may have shaped the associations found in this study between EOCU and the failures to complete or achieve each of the educational milestones beyond primary school. This is mainly because, for each of the associations in aim 3, the study populations varied to only include those at risk of failing to achieve each of the studied educational milestones. For example, the study population for failing to complete secondary school included only respondents who at least got to enter into secondary school, excluding those who did not go beyond completing primary school at the time of the interview. This procedure then created a highly selected sub-population in which the

association between EOCU and failing to complete secondary school was studied. This over-selection of people leads to a more homogeneous population who got to make it to the path of secondary school, leaving out people in more disadvantageous conditions who did not enter school or did not go beyond completing primary school. The strength and direction of the associations between EOCU and failing to complete secondary school can be shaped for this over-selection of the population where these associations are studied.

Some readers may have concerns on two accounts: 1) that the association between EOCU and failing to complete educational milestones that this study finds may have existed from the very beginning due to other early in life factors that cause both outcomes (i.e., confounding effect), and 2) that a lack of association may be due to an attenuation of the effect given the exclusion of people who did not enter into secondary school after completing primary school as they are not a random sample of the general population, mainly due to factors of social disadvantage that in turn are also associated with cannabis use.

So, to address concerns involving the possibility of an over-selection that leads us to see spurious associations or a lack of association between EOCU and each of the educational milestones, I set up aim 1 and aim 2. Specifically, these two aims address the concern that the two variables are socially-disadvantageous events that can be caused by similar adverse events happening very early in life, and the concern regarding the possibility of an over-selection that can also have pulled the statistical estimate of association towards the null as it takes out those who are socially disadvantaged from the very beginning.

Therefore, Aim 1 and Aim 2 explored whether the association between EOCU and schooling attainment exists even for the earlier milestones of education. This association was

plausible because very early adverse events in life might affect a poor trajectory for schooling and might affect becoming a case of EOCU. Alternately, individuals with personality traits or behavioral characteristics such as conduct problems or attention deficits with hyperactivity are more likely to engage in problematic behaviors early in life (such as cannabis use) and also have a very poor schooling trajectory, especially among those who are socially disadvantaged. To assess the potential that an over-selection of people may shape the associations for aim 3 seen in this study, I looked for evidence that an unfortunate schooling trajectory is associated with EOCU, mainly failing to enter primary school, which is an event that happens very early in life. If the two are associated, I can suspect there may be background characteristics that are shaping the association between EOCU and the schooling trajectory from the very beginning, in the earlier stages of life, and that the same association can be kept all across the stages of the individual´s life and presented even in over-sampled populations like those used in the present study, (i.e., the population of people that entered high-school, that completed high school and that entered tertiary school). In this study, when this association was explored, after adjusting for sex and age, the initial association in the crude analysis disappeared. To exemplify this finding, I can refer to aim 1, where I found, after taking into account sex and age, that people who did not enter primary school had the same probability of early cannabis use as those who achieved higher educational milestones, such as completing college.

Specifically, results from Aim 1 and Aim 2 showed, as expected, that sex and age are robustly and precisely associated with school entry. However, the cannabis estimates have no robust or precise association with early milestones of educational achievement in the analyses. These findings suggest that events associated with the sociodemographic circumstances that a person encounters very early in life are the ones that shape both cannabis use and school entry,

which in turn seem to be independent of one another. Consequently, these results do not support the hypothesis that failure to entry in the school trajectory increases the risk of any cannabis involvement.

The association between EOCU and failing to complete each of the milestones studied in this dissertation is consistent with the hypothesis that cannabis causes those outcomes, but it is not the only potential cause, as I discuss later. However, at this point, from aim 1 and aim 2, it can be said that there is no evidence that the association between EOCU and the school trajectory is already shaped before people get to secondary school and further schooling stages.

5.1. Study 1: Cannabis use and school entry

5.1.1. Interpretation of key findings

This aim specifically assesses the possibility that events happening very early in life (i.e., happening before 5 years), or that impact the first years of life, which include factors related to genetic or familial background, put individuals at a higher risk of both failures to enter into primary school and cannabis use in general, and EOCU in particular. I found no evidence for this assumption.

5.1.2. Comparison to previous studies

Some evidence that links these two adverse life events as a consequence of genetic and familial factors has been presented by Verweij et al. (Verweij et al. 2013). These authors carried

out a study in a sample of 3337 adult twins drawn from the Australian Twin Registry to look for evidence consistent with the hypothesis that EOCU and poor school trajectory are associated beyond the effect of genetic and environmental factors that an individual finds early in life as a product of what James Heckman calls the accident of birth (J. J. Heckman 2013b). This study found that the association between EOCU (defined as use that started before age 18) and poor educational attainment was more likely because of familial shared factors, mainly those with an environmental origin (Verweij et al. 2013). However, some limitations of Verweij's study need to be taken into account before being considered as definite evidence. One of the main limitations, which has not been mentioned by Verweij et al., has to do with the large proportion of people who use cannabis among the twin population (i.e., 76.6% among males and 64.9% among females) which translate into a corresponding proportion of people who started early use of cannabis (i.e., 44.8% among males and 32.9% among females). Similar results were found by Grant et al. (2012) in a sample of 6242 twins of males, veterans of the US military that have been beneficiaries of educational benefits after their serving time during the Vietnam period. Specifically, these authors found that twins pairs who were discordant regarding cannabis use, age of onset of cannabis use, and cannabis dependence did not differ in education level. These findings support the hypothesis that the association between cannabis use and educational attainment is due to the influence of family factors rather than a direct causal link between both variables (Grant et al. 2012).

These estimates suggest that cannabis use is widespread in the society where the study was performed and contrasts with a rather low occurrence of early school leaving in the same study population. As Rose (2001) aptly puts it, "the more widespread is a particular cause, the less it explains the distribution of cases" (Rose 2001).

The high prevalence of cannabis use in Australia, especially use that starts before 18 years, contrasts with the small proportion of people who do not complete secondary school (defined as 12 years of school). The rather unusual nature of failing to complete secondary school in this country is explained by how the educational system is arranged in Australia where everybody is obliged to complete at least ten years of school. This allows the majority to complete 12 years of schooling, including the last year of secondary school. Therefore, the large proportion of cannabis use starting before age 18 and the small occurrence of poor educational attainment in Australia may have blurred the effect of cannabis use and failure to complete secondary school among twins found by Verweij et al., leading them to conclude that the association was consistently seen in several other studies in other contexts between EOCU and poor schooling is explained only by environmental factors occurring in the first decades of the life of individuals (Verweij et al. 2013).

Another type of evidence that goes along the lines of this hypothesis addressed by Verweij et al. is an assessment of the way in which adverse events happening in the pre-school age make people more prone to a higher risk of poor school attainment and cannabis use starting early in life (Verweij et al. 2013). There is plenty of evidence that adverse environmental circumstances occurring between the birth and the fifth year of life can shape the schooling trajectory as well as other social- and health-related aspects of an individual´s life. Although literature on how adversities affecting child development are associated with the risk of early cannabis use is scarce, there is plenty of evidence that these early events increase the risk of poor educational attainment, crime, teenage pregnancy, and lower-income as well as poor health, many of which have been found to also be associated with early cannabis use (J. J. Heckman 2012).

5.1.3. Study strengths and limitations

In this study, I did not find evidence that entry into the school trajectory is associated with cannabis use, after taking into account the effect of two key demographic characteristics (age and sex), which have a well-known effect on both the occurrence of drug use and school attainment. The reason sex is taken into account is that in some countries, women are still in a disadvantaged social position that makes them less likely to progress along the education pathway. Similarly, research shows that males are much more likely to use illegal drugs. Age is a proxy to trace back the possibility of cohort effects given that, along the years, countries may have experienced cultural and political changes that may have affected both cannabis use and school attainment.

The main limitation of this study has to do with the cross-sectional design that does not allow us to be certain about the age of first use of cannabis. Some information misclassification is possible as the age of first use of cannabis was asked a long time after it occurred. However, there is no reason to think that those entering school (from primary school onward) are more or less probable to be able to recall this information than those who did not enter school. In this sense, I believe the information misclassification is balanced regarding the age of onset of cannabis use.

On the other hand, one of the main strengths of this study has to do with the type of statistical analysis used to derive the estimated associations between entry school and cannabis use. I used the conditional logistic regression matched by the area of residence at the time of the interview. This method allowed me to hold constant country-related cultural, legal, and political aspects that might affect school attainment and drug use. However, some researchers may have questions about the pertinence of this type of geographical matching based on where the participant lives at the time of the interview, which is likely to be different than the place where he or she

lived during the first decades of life. Although it would be ideal to perform an analysis using as a matching variable the geographical area where the individual lived during adolescence, this is very difficult to perform. First, most cross-sectional studies do not gather information about places where the participant lived across their life stages, and even if this were possible, one would need to have several people available for the variable of interest to ensure matching. Second, most studies derived from cross-sectional multi-staged designs and case-control designs use the place where the participants were enrolled as the matching variable and not the place where they probably were exposed to the suspected cause early in life. In this sense, to use the variable of the area where the participant was drawn from and not the place where the participant was exposed to the suspected cause is well accepted by the scientific community as a method that derives valid statistical estimations of association.

5.1.4. Implications and future directions Aim 1

This study implies that there is no evidence to support the hypothesis that early in life environment aspects affecting the probability of entering school are also affecting the probability of using cannabis, including that use that starts early in life, once sex and the birth cohort effect are controlled for. All of this suggests that if any associations appear later between EOCU and failure to complete secondary school and the subsequent educational milestones, these associations are most likely not due to a remaining effect of factors present in the very early years of the life of the individual that persist for "survivors" who make it to secondary school and beyond.

5.2. Study 2: School trajectory and early-onset cannabis use

5.2.1. Interpretation of key findings

This aim explored the possibility that events happening in an individual´s life during the early stages of school may be responsible for EOCU among people who achieved any particular school level. For this study, I chose three reference groups with a key meaning in the school trajectory as they have been consistently related to social and health achievements later in life. These reference groups include i) those who did not enter into primary school, ii) those who completed secondary school, and iii) those who completed tertiary school.

Compared with those who did not enter into primary school, after a basic adjustment that takes into account the potential confounding effects of sex and year of birth, there was no difference in the probability of being an EOCU for those who achieved higher educational attainment, including separately those with some primary, complete primary, some secondary, complete secondary, and some or complete tertiary school.

This finding shows that the probability of being EOCU for those achieving all the educational milestones is similar to those who did not enter school. This is consistent with the findings from aim 1, where I took all the school levels as a unique group and not separately, as has been the case in this study (aim 2). I was expecting to find differences at least for the most dissimilar groups -- for example, between the group of those who did not enter into primary school and those who completed secondary school. This was not the case, which brings further evidence that EOCU may not be associated with adverse events happening very early in the individuals' life which are known to have the potential to impede progress in educational attainment.

However, to look at people who did not make it at all to the school trajectory only addresses the eventuality that extreme adverse events happened very early in the individual's life (i.e., the first 5 years of life), but does not address the situation where these events happen later, e.g., between 6 and 16 years of age. In fact, this is the age where some personality traits and other factors that affect the individual's behavior or their social well-being can shape the probability of both a poor school trajectory and a propensity toward illegal drug use. This would be the case, for example, for children with ADHD or other conduct problems, who are at higher risk of both poor academic outcomes and substance use, in particular, cannabis use.

To better see the way life events that happen after the individual enters school shape the probability of attaining higher levels of education and starting to use cannabis, I used as a reference group those who successfully complete tertiary school. By doing this, and taking into account variables that may confound the association, all the levels of schooling, once the person begins school, were associated with a higher probability of starting cannabis use before age 17.

This analysis presents evidence that there are factors in the life of people after they begin schooling that impede the individual´s progress beyond primary school and make them more likely to use cannabis before age 17. The effect of such factors is beyond the effect of other factors measured in this study. These factors included sex, birth cohort, conduct problems, attention and deficit traits, history of victimization or witnessing several types of domestic violence, the early onset of cocaine, and other illegal drugs as well as the extramedical use of prescription drugs, parental education, and parents' mental health.

Therefore, compared with those who achieved the highest educational milestone (i.e., completing tertiary school or more), those who just completed primary school, or made it up to

some secondary school, or completed secondary school, or achieved some tertiary school were more likely to have started cannabis use before age 17 (EOCU). In contrast, the probability of being EOCU among those who did not enter into the school trajectory or only completed some primary school does not differ from those who completed tertiary school. All of these findings are independent of the effect of meaningful covariates that trace back adverse circumstances happening during childhood or early adolescence of individuals. These findings go along with the hypothesis that an early-in-life involvement with cannabis may have a role in not reaching the highest educational milestone. This correlation remained after adjusting by confounders that influence the occurrence of both variables. This brings more empirical evidence in favor of a causal relationship between these variables.

However, some researchers may argue that the use of the group that completed tertiary school as a reference group may inflate differences as this is the most advantaged social group. Also, as this is not the most common educational milestone achieved for most people in the countries under study, to use this group as the reference group may hide useful epidemiological information linking the early onset of cannabis use and the failure to achieve the most common educational milestone achieved, i.e., secondary school.

Thus, as shown in the frequency tables in this study, the highest educational milestone achieved in most of the studied countries is completed secondary school. As a result, I set up an analysis to see how EOCU is associated with educational milestones below completing secondary school. Given the large body of evidence showing that incomplete secondary school is related to social and economic limitations later in life, it is advantageous to take those who completed this milestone as a reference group. Furthermore, this action may help shed light on events happening

in the individuals' lives between entering school and completing secondary school, making them more likely to fail to finish secondary school and start using cannabis early (i.e., before age 17).

In this regard, I found that after taking into account the effect of the birth cohort and sex, those who have at least some primary school were more likely to start cannabis use before age 17 compared to those who completed secondary school. The evidence that EOCU has similar occurrence distribution among those who completed secondary school and those who did not enter into primary school suggests that the factors that shape the probability of not entering into the school trajectory are independent of those that influence the probability of starting the use of cannabis before age 17.

Also, in this analysis, I found evidence that suggests that those who get to progress from completing secondary school to achieving some degree of tertiary school or completing it are less likely to start using cannabis before age 17. This finding is evidence against the argument suggesting that cannabis use is more likely in more socially advantaged individuals who, in turn, achieve higher educational levels in life.

5.2.2. Study strengths and limitations

In this study, the limitations are the same as in the first study of this dissertation (which addresses Aim 1). However, in this study, I have the additional limitation that has to do with a necessary condition for schooling progression: namely, that in order to pass to the next level of education, you have to complete the previous one. In other words, for this study, there is no exclusion of those who are no longer at risk for failing to complete the higher educational levels.

For example, in order to be able to complete secondary school, an individual has to have entered primary school, completed primary, and entered into secondary school. This means that the natural comparison group necessary to identify factors associated with the probability of completing secondary school is all people who have some secondary education, excluding the groups who have some primary, or who have completed primary as they are no longer at risk of failing to complete secondary school. Instead, I have taken for Aim 2 separately all the education groups at once just to have a sense of the general association between EOCU and education level, but not to see if this variable may put people at higher or lower risk for failing to complete secondary school, enter or complete tertiary school. Aim 3 of this dissertation (presented in the next section) is designed to address this issue.

5.2.3. Implications and future directions

In this study, the main finding is the lack of associations between early-onset cannabis use and not making it beyond primary school. This finding suggests that in general, very early circumstances in life that affect the early phases of the school attainment are independent from those that increase the probability of starting cannabis by age 17. This evidence suggests that any association between early-onset cannabis use and failing to complete secondary school or further educational milestones may be the result of a causal correlation or the result of common factors happening after the individual gets into primary schooling.

5.3. Study 3: Early-onset cannabis use and achievement of educational milestones beyond primary school

5.3.1. Interpretation of key findings

In this study, I found evidence that the use of cannabis that starts before age 17 is clearly, consistently and independently associated with failing to complete secondary school by age 18 among people who made it into the secondary school. I also found evidence, albeit inconsistent, that the early onset of cannabis use is independently associated with failing to enter tertiary school by age 21 among those who completed secondary school and with completing this school milestone by age 25 among those who make it to tertiary school.

The multinational nature of the study, along with using different statistical methods that hold constant the effect of several potential confounding variables such as place of residence, sex, age, conduct problems during childhood or adolescence, hyperactivity and attention problems during childhood, illegal drug use of early-onset, and other childhood life circumstances, supports the notion that EOCU increases the risk of failing to complete secondary school once the individual enters secondary school.

Cannabis and culture or social context: There is an evident cross-country variation in the association size between EOCU and each educational milestone studied. This variation suggests a sociocultural effect shaping the relationship between early-onset cannabis use and the achievement of educational milestones. For example, for completing secondary school, both in the adjusted conditional and unconditional logistic regression models, this study found that, in general, ECOU appears associated only for American countries and Israel, but not for the European and African countries that have enough cases to derive statistical estimates. In the case of entering tertiary

school after completing secondary school, EOCU appeared as a consistent independent predictor only for the USA, and for completing tertiary school after initiated it, only for Colombia and the USA. For the rest of the countries, the statistical association was lost even after adjusting by age and sex.

Therefore, even though the pooled results show a consistent robust association between EOCU and failing to complete secondary school, it is worth noting that the USA largely drives this estimate. Thus, I decided to estimate the association between early-onset cannabis use and each school milestone studied in the WHMS participating countries other than the USA. I found that the probability of failing to complete secondary school remained approximately the same after excluding the USA, while the estimates for that country alone were similar, although somewhat smaller than in the pooled estimate. Therefore, the evidence indicating that early-onset cannabis use is associated with a higher probability of not completing secondary school is robust, and that association is consistent across the countries where cannabis use is not a rare condition.

On the other hand, the results for EOCU and failure to enter college are quite heterogeneous across countries (weak positive association for the USA [OR=1.3] and rather strong but imprecise associations in Italy and Netherland [OR=0.2 and 0.3]). Although the pooled estimate derived from the unconditional-derived estimates meta-analysis turned out to be not robust or precise, the estimate derived from the conditional logistic model was robust or precise. This is because of the influence of the USA, as judged by the analysis where this country was excluded. Thus, while in the USA, the use of cannabis that started early in life was associated with failing to enter into college after completing secondary school, this association does not hold for the remaining countries taken together. I suspect that cultural differences may be the primary explanation for these results, especially after acknowledging that cultural and social factors, including those

derived from the legal arena, play a vital role in drug use behaviors. That none of the Asian countries in the WMHS had enough cases to produce meaningful estimates is an example of how much these behaviors (or reported behaviors) vary across countries. Future studies are needed to explore the underlying mechanism or factors that could account for these observations.

5.3.2. Study strengths and limitations

Before detailed discussion of these results, which have been obtained using data from 16 countries, gathered through population-based studies using overall similar epidemiological methods of probabilistic sampling and standardized instruments, several of the more important study limitations merit attention. The first limitation has to do with the cross-sectional design of the study, which did not allow for the assessment of temporal associations between the time of initiation of cannabis use and the moment in which individuals dropped out of school. In fact, it could be the case that an individual dropped out of school in a specific month of a given year but started to use cannabis soon afterward, in the following months of the same year. In this case, an association can appear in the statistical analysis between the EOCU and dropping out of school, but still, the former may have happened after the latter. These findings are consistent with longitudinal findings performed in developed countries, such as the study by Ryan (2010) (Ryan 2010; David M. Fergusson and Boden 2008).

An additional limitation involves the lack of data regarding the level of cannabis use. The WMHS data include neither information about the frequency, intensity, and period of time in which the use of any of the illegal drugs studied occurred, nor information about the individual meeting criteria for drug abuse or dependence for cannabis. As this type of information was not

gathered in the WMHS, it was not possible to link school dropouts to heavy cannabis use or dependence. Although this information would have enriched the study with ways to explain in a plausible way how cannabis use leads to school dropouts, heavy cannabis use and dependence are public health priorities in their own right and should be the target of interventions that reduce their burden of disease. At present, however, few people, including physicians and other health professionals, recognize that even a single use of cannabis can place people at higher risk of social inequalities such as poor schooling trajectories. This is important from the public health perspective as ever use of cannabis can be more easily identified through extended population-based programs than abuse or dependence, especially among young people. This makes ever cannabis use a promising indicator to direct the actions to teenagers at risk of dropping out of school, probably because of cannabis use by itself.

The evidence is consistent with the notion that the earlier the drug use starts, the more likely the user is of becoming an abuser or dependent on the substance (C.-Y. Chen, Storr, and Anthony 2009). This evidence means that people who start to use cannabis as early as during schooling, especially before completing high school, are more likely to have heavier use, which also means they are more likely to experience more cannabis use-related problems, including abuse and dependence. This is consistent with our findings where EOCU are more likely to drop out of school, probably through a heavier involvement in the use of this substance.

Another limitation is that the WMHS does not ask for detailed information about the use of alcohol and tobacco when the individual is in each period of schooling. Although there are data on alcohol and tobacco use regarding the age of onset, lifetime abuse or dependence, and age of the first episode of these types of disorders, there are no data that systematically asked for each schooling period. In addition, most people who have used cannabis before 17 have used alcohol

or tobacco by that time. This fact has made it challenging to include abuse or dependence on alcohol or tobacco in the model to assess the independent effect of EOCU on the probability of dropping out of high school and further steps in the schooling trajectory. However, it was possible to adjust by the early-onset use of these commonly used substances and other 16 covariates, strengthening the confidence of an independent association between EOCU and achieving the educational milestones beyond entering secondary school.

Among other limitations, there may be memory-related misclassification issues, mainly on reporting the age of onset. Although this can be present especially among the older people, there is no reason to believe that those with poor schooling trajectories would recall differently than those with better trajectories, which makes the possibility of recall bias unlikely. The resulting balanced misclassification error could be responsible for pulling the estimated associations toward the null.

Another limitation has to do with the lack of information about the location of exposure where the first use of cannabis occurred. Ideally, it would have been advantageous to have this geographical information and thus be able to match each case of early onset of cannabis use with a control that shared the cultural and sociopolitical context that shaped the probability of using cannabis and the educational trajectory of the individuals concerned. Instead, we have matched cases to controls based on the location information at the time of the interview, which for most people is very likely different from the place where the individual was at the moment he or she started to use cannabis. This means that the matching for this study is limited regarding its effectiveness in holding constant strong potential cofounders that influence the risk of starting the use of cannabis early in the life of individuals as well as the probability of achieving school milestones. I acknowledge this limitation, but it is a step toward future research, where it may be

possible to have a time-varying covariate to indicate how many times (if at all) the respondent had moved from the area of residence during cannabis-using years. This variable was not in the WMHS datasets, and I rely, in the same way as many other case-control design studies, on a pair-matching based on the location at the moment of interview, which can help to control some early-in-life variables that eventually determined where the people live during adulthood through its influence over life events that are related to factors influencing education achievements as well as other socially crucial outcomes. Although imperfect, the matching for the case-control design in my study is a step forward in understanding the relationship between early onset of cannabis use and educational attainment, holding some contextual characteristics related to the place where the person ends up living during a certain point during their adulthood.

The use of conditional logistic regression in the context of a three-staged, probability-sampled, population-based study is that probability weights cannot be incorporated in the model also constitutes a study limitation. Therefore, the results may be somewhat biased if non-participation is related to cannabis use, level of education, or other confounding variables that affect both cannabis use and level of education, especially for countries with low participation levels.

Finally, the problem of the 'omitted variables' or 'model misspecification,' where unmeasured confounder variables were not considered in the statistical model, leading to spurious results. For example, as suggested by one of my committee members, I want to draw attention to the importance of cross-generational wealth or family wealth in studying the potential effect of cannabis use on educational achievements. There is some evidence that relates the family wealth context in which a child is born and raised and the level of education he reaches later in life, especially completing tertiary education (Pfeffer 2018)(Hällsten and Pfeffer 2017)(Chesters 2019).

Given that transgenerational wealth may influence educational attainment and may indirectly influence risky behaviors, such as cannabis use, it can be worth considering, as confounding variables, indicators of family wealth. However, I have not found a cannabis use study that has taken care of measurements, as covariates, of what grandparents or parents provide to the children, for example, in the form of Trust funds or endowments, that would help the children, or the grandchildren, be successful in their education beyond free public school. This is an unexplored area of research in cannabis use and its psychosocial effects that deserves greater attention as countries become increasingly wealthy and grandparents begin to make this type of investment in the future of children's education.

5.3.3. Implications and future directions:

The aim 3 of this dissertation found that there is consistent observational evidence supporting the hypothesis that the use of cannabis may disrupt completing secondary school. However, the evidence supporting a potential causal association between EOCU and entering or completing tertiary school is still weak. More studies are needed to confirm this association.

It may be premature to assert that these findings have practical implications for clinical practice or in public health work. The next steps must include more research before advocating change in current practices. Truly definitive evidence on this suspected causal association between EOCU and failing to achieve educational milestones may require completion and replication of experiments where the power of randomized assignment to early interventions can be used to prevent or disrupt the occurrence of early-onset cannabis smoking with an expectation of improved educational trajectories. Thus, the most important next step in research is to perform randomized

trials, mainly in the form of community trials, aimed to test measures that delay the onset of cannabis use and see if that has an impact on improving completion of educational milestones beyond primary school.

As Hasin D suggests in a recent paper, it is vital to be aware of the potential consequences of the recent changes in the legislation regarding the use of cannabis in many parts of the world, as is the case, for example, in the USA (Hasin 2018). Although research efforts have started to generate evidence about the potential impact of the implantation of medical and recreational marijuana laws, many gaps of knowledge remain to be covered, mainly regarding the impact of those laws that have decriminalized the recreational use of cannabis. Specifically, as Hasin D (2018) concludes, the evidence is consistent that there is no effect of medical cannabis laws on adolescent cannabis use, but still, very little is known about the potential effect of the recreational marijuana laws and the use in adolescents. Although this scarcity of evidence is mainly because these kinds of laws have only very recently started to be enacted, Hasin D points out that the existing evidence is inconsistent. Thus, some studies show that recreational marijuana laws were related to a decrease in the perception of harmfulness of the use of cannabis among adolescents as well as with an increase in cannabis use; other studies show no such associations. Besides, there is a large room for concern given that recreational marijuana laws may likely increase availability and access to cannabis through widespread advertisement, social acceptance of the general population, and reduced prices. All of this yields the recommendation that research regarding any causal relationship between adolescent cannabis use and educational milestone failures continue, as well as research aimed to identify the mechanisms involved in case these two variables are causally related. If indeed they are causally related, it can be expected substantial challenges for

societies with these types of laws, which should put in place measures to mitigate the impact of EOCU on the educational trajectories of individuals.

CHAPTER 6. CONCLUSIONS

This dissertation research project is based on cross-sectional epidemiological field survey data gathered in 16 countries where World Mental Health Surveys had been completed between 2001 and 2007. The project estimates included two aims intended to set up the problem of studying the degree to which early-onset cannabis smoking might predict or account for failure to live up to expectations for educational attainment. It was thought to be necessary to complete work under the first two aims to make a more comprehensive interpretation of the estimates produced under the third aim.

That is, the central focus of the project is on the possibility that cannabis smoking, early in life, might disrupt the trajectory of young people as they enter secondary school, and seek to live up to their expectations, and their families and society's expectations, about their future success in secondary and post-secondary school. This focus is the central topic for the project's third aim, but to interpret the estimates for this aim, it seemed necessary to check (1) whether there might be an association between early cannabis smoking and failure to enter into school at all, and (2) whether there might be an association between cannabis smoking and level of educational attainment, observed cross-sectionally. By looking into whether cannabis smoking is associated with level of education, and by checking for the possibility that cannabis smoking disrupts school entry entirely, I have been able to make a more complete interpretation of the estimates on the possibility that early-onset cannabis smoking has been disruptive to achievement of the later milestones of secondary and post-secondary schooling.

In the work conducted under specific aim 1, the crude conditional logistic regression model with matching for site and area of residence but with no statistical adjustment for age and sex produced a somewhat misleading result that might lead one to suspect that history of cannabis smoking protects against failure to enter into the schooling trajectory. This misleading result can be traced back to the cannabis history and the schooling history of different age strata. A simple statistical adjustment for sex (being male) and age disclosed the potential error of inference. Once covariate terms for sex and age are added to the conditional logistic regression model, there is no association. Furthermore, the work under aim 1 sought to estimate the strength of association between failing to enter school at all and the odds of starting to smoke cannabis early in life (before age 17 years). In the principal cross-sectional analysis, again with area-matching and the conditional logistic regression model and covariate-adjustment for sex and age, there was no association. Post-estimation exploratory analyses were used to address a measurement issue related to potential unreliability or invalidity in reporting the age of onset of cannabis smoking; the odds ratio estimates and conclusions from this post-estimation exploratory analysis were not appreciably different from the estimates and conclusions of the primary analysis under this aim.

Furthermore, in Aim #2 completed before estimating a suspected causal association that links early-onset cannabis smoking with later failure to achieve social expectations in school, I did not find evidence suggesting that those who did not make it into even primary school are in a higher risk of starting to smoke cannabis before age 17 years than those who i) entered into primary school but not secondary school, (ii) secondary school but not completed it, (iii) those who completed this education level but did not make it to post-secondary education, (iii) those who entered into tertiary school, and (iv) those who completed it. Moreover, I did not find evidence suggesting that those who make it to primary school and complete it are at higher risk of starting

cannabis use before age 17 than those who complete secondary school. However, compared to those who went up to the highest educational level, those who did it into the schooling trajectory up to some tertiary school are at higher risk of being an early-onset cannabis use but not those who did not enter primary school. This finding is consistent with the notion that EOCU and factors that lead to poor educational trajectory coincide with the schooling age, which rejects the idea that factors happening very early in life may be shaping the association between EOCU and poor educational attainment.

Having clarified null associations between aspects of cannabis smoking history, school entry and levels of early education, where common adversities in life may influence both the probability of early-onset cannabis use and the probability of not achieving the educational milestone after primary schooling, it was possible to complete the work under Aim 3, with a focus on the large sub-population of study participants who had entered secondary school. The first sub-aim under Aim 3 was to estimate the degree to which the history of early-onset cannabis smoking might predict or account for failure to complete secondary school, once secondary schooling had started. Based on the area-matched conditional logistic regression model with statistical adjustment for sex and age, there was an apparent prediction from early-onset cannabis smoking to later secondary school failure for the American countries, Belgium, and Israel ($p < 0.01$). This predictive association was attenuated only for Colombia, the USA, and Israel with statistical adjustment for the complete set of eighteen covariates, such as early-onset substance use, youthful conduct problems, and other variables. The meta-analytic odds ratio estimate was 1.9 (95% CI = 1.3, 2.7). When using the estimates derived from the full-adjusted unconditional logistic regression, the resulting meta-analytic odds ratio estimate was 1.9 (95% CI = 1.4, 2.7).

Concerning failure to enter into post-secondary schooling once secondary schooling has been completed, the history of early-onset cannabis smoking again was predictively associated with non-progression of schooling trajectory. In this instance, the odds of failing to enter post-secondary education was elevated among early-onset cannabis smokers in area-matched analyses with the complete ser of covariate terms in the conditional logistic regression model (meta-analytic odds ratio estimate of 1.4; 95% CI = 1.1, 1.7). For 13 countries, it was possible to produce country-specific sample-weighted estimates for this association using the unconditional form of multiple logistic regression and the same set of covariates (e.g., including youthful conduct problems). In this instance, the resulting meta-analytic odds ratio estimate of 1.1 did not help to confirm the results from the prior conditional logistic regression model (OR = 1.2; 95% CI = 0.8, 1.8).

For failure to complete tertiary schooling once it has started, the history of early-onset cannabis smoking was again predictively associated with non-progression of schooling trajectory. In this instance, the odds of failing to complete post-secondary school were marginally elevated among early-onset cannabis smokers in area-matched analyses with the eighteen covariate terms in the conditional logistic regression model (meta-analytic odds ratio estimate of 1.3; 95% CI = 1.0, 1.6). However, for only four countries, it was possible to produce country-specific sample-weighted estimates for this association using the unconditional form of multiple logistic regression and the same set of covariates. The resulting meta-analytic odds ratio estimate did not help confirm the prior conditional logistic regression model result (OR = 1.2; 95% CI = 0.7, 2.0).

These results are important because they have broadened the base of evidence about the possibly-harmful effects of early-onset cannabis smoking concerning educational outcomes and schooling trajectories. Nonetheless, truly definitive evidence on this suspected causal association may require completion and replication of experiments where the power of randomized assignment

to early interventions can be used to prevent or disrupt the occurrence of early-onset cannabis smoking, with later follow-up of the experimental participants and an expectation of improved educational trajectories in the participants who benefit from the early intervention.

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