Published in final edited form as:
Addict Behav. 2010 January ; 35(1): 35–41. doi:10.1016/j.addbeh.2009.08.006.

A Cotwin-Control Analysis of Drug Use and Abuse/Dependence Risk associated with Early-onset Cannabis Use

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Abstract

We assessed whether, after controlling for genetic and shared environmental influences, early cannabis use remains a significant predictor of other drug use, abuse, and dependence, and whether the risk for early users is greater than that for later cannabis users. Data from a 1992 telephone diagnostic interview of 8169 male twins (M = 42.0 years at interview) who served in the U.S. military during the Vietnam-era were used to identify a subsample of 293 monozygotic (MZ) and dizygotic (DZ) twin pairs discordant for early cannabis use (before age 18). Using cotwin-control analyses, outcomes assessed were: lifetime illegal drug use (stimulant/cocaine, sedative, opiate, and hallucinogen/PCP), lifetime DSM-III-R illegal drug abuse/dependence, and lifetime DSM-III-R alcohol dependence. After controlling for covariates, early cannabis users were at greater risk than their later/never-using cotwins for 8 of 9 substance-related comparisons, including: using other illegal drugs (ORs: 2.71-4.09), having illegal drug abuse/dependence (ORs: 2.02-2.13), and developing alcohol dependence (OR=2.36). When analyses were limited to pairs in which the cotwin used cannabis later, early and later users only differed significantly on sedative, opiate, and hallucinogen use. After familial influences on early cannabis use were controlled for, cannabis use—regardless of the age of initiation—still conferred increased risk of other illegal drug use, drug abuse/dependence, and alcohol dependence. In contrast to previous research, there is limited evidence for increased risk associated with early-onset use in this sample of Vietnam-era veterans.

Keywords

early cannabis use; cotwin-control; drug abuse/dependence; alcohol dependence

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1. Introduction

Cannabis is the most commonly used illegal drug in the United States (Johnston, O'Malley, & Bachman, 2003), and research has consistently indicated that cannabis use is associated with an increased risk of other illegal drug use and problems (Donovan & Jessor, 1985; Hammer & Vaglum, 1990; Jessor, Chase, & Donovan, 1980; Kandel, Davies, Karus, & Yamaguchi, 1986; Kandel, Yamaguchi, & Chen, 1992; Morral, McCaffrey, & Paddock, 2002). Furthermore, multiple studies have shown that the risk of substance abuse/dependence is greater among early illegal substance users than among later-users (Anthony & Petronis, 1995; Grant & Dawson, 1998; Hall & Lynskey, 2005; Lynskey et al., 2003).

There are several plausible explanations for the association between early cannabis use and later other drug use and problems. One possibility is that cannabis serves as a “gateway” to other substance use and problems, and that earlier onset increases the likelihood of progression to problems (Hall & Lynskey, 2005; Kandel, 2003a, 2003b; Kandel et al., 1992; Pedersen & Skrondal, 1998). Alternatively, it is possible that both early use and the development of later problems are influenced by an underlying shared vulnerability (Morral et al., 2002), which may be genetic and/or environmental. There is evidence of familiality for cannabis use, abuse, and dependence (Kendler, Karkowski, Neale, & Prescott, 2000; Lynskey et al., 2002; Maes et al., 1999; Rhee et al., 2003; Tsuang et al., 1999), and that familial influences on cannabis abuse/dependence overlap with the influences on other drug abuse/dependence (Fu et al., 2002; Kendler, Jacobson, Prescott, & Neale, 2003; Kendler, Myers, & Prescott, 2007; True et al., 1999; Tsuang et al., 1998; Xian et al., 2008).

In the current paper we use a cotwin-control design to explore whether early-onset cannabis use is associated with increased risk of other illegal drug use, alcohol dependence, and illegal drug abuse/dependence in a sample of U.S. Vietnam-era veteran male twins after controlling for latent familial vulnerability. Two separate cotwin-control analyses were conducted: 1) using pairs in which one twin used cannabis early and the other either used cannabis later or never used cannabis, and 2) restricting the data to the subset of discordant pairs in which the cotwin later initiated cannabis use. The first analysis addresses discordance at the population-level (in which some individuals use later and others never initiate), and the second addresses discordance for age of initiation among users. Previous cotwin-control analyses have indicated that there are individual-specific influences that put early cannabis users at greater risk of other drug use, abuse, and dependence relative to those who do not use cannabis early (Agrawal, Neale, Prescott, & Kendler, 2004; Lessem et al., 2006; Lynskey et al., 2003; Lynskey, Vink, & Boomsma, 2006). However, only Lynskey et al. (2003) and Agrawal et al. (2004) compared early users not only to both later/never users but also restricted to later users. Replication of this observed association in a variety of samples is required, as it is possible that associations may vary across age, birth cohort, and/or culture.

2. Methods

2.1. Sample

The present sample was drawn from the Vietnam Era Twin Registry (VET-R), a national register of 7375 male-male twin pairs in which both members served in the military during the Vietnam-era (i.e., between 1965-1975). The construction of the Registry and the method of determining zygosity have been described in detail elsewhere (Eisen, Neuman, Goldberg, Rice, & True, 1989; Eisen, True, Goldberg, Henderson, & Robinette, 1987; Henderson et al., 1990). In 1992, 8169 individuals in the Registry completed a telephone diagnostic interview that included lifetime assessments for a number of psychiatric disorders, including abuse of/dependence on alcohol and illegal drugs (Tsuang et al., 1996, 1998). Telephone interviews were conducted by experienced interviewers from the Institute for Survey Research at Temple

University, and interviewers obtained verbal informed consent as approved by the relevant Institutional Review Boards before conducting interviews. Of the 3934 individuals who had used at least one illegal drug, 95% used cannabis before any other illegal drug, 4% used cannabis only after using another illegal substance, and only 1% never used cannabis. Because early cannabis initiation was used as a predictor for other drug use and abuse/dependence, the present analyses included only the 6362 individuals from complete twin pairs in which *neither member* used another illegal substance or developed alcohol dependence prior to cannabis initiation (89.9% of complete twin pairs in the sample). At the time of interview, the respondents had a mean age of 42.0 years (SD=2.8) and most were married (77%). Based on military record data, 94% of the respondents were Caucasian, with 6% being African-American and <1% being of another ethnicity. Additional data on education (available for 96% of the respondents from a self-report questionnaire) indicated that in 1987, 3% had less than 12 years of education, 31% had 12 years of education, and 66% had some education beyond high school.

2.2. Measures

2.2.1. Early cannabis use—Early cannabis use, defined as cannabis initiation prior to age 18 (i.e., age 17 or under), was the primary predictor for drug-use outcomes. Initiation prior to age 18 was selected because: (i) it meant that cannabis initiation occurred prior to military enlistment, while respondents were likely still in high school and living at home, and (ii) only 19.1% of cannabis users (n=539 respondents; 8.5% of the full sample) were “early” cannabis users based on this cutoff, suggesting use prior to age 18 was “early” for this cohort.

2.2.2. Lifetime drug use and abuse/dependence—Indices of illegal drug use and abuse/dependence and alcohol dependence were collected in the 1992 telephone diagnostic interview, based on the Diagnostic Interview Schedule (DIS-III-R) (Robins, Helzer, Cottler, & Goldring, 1989). For cannabis, cocaine, stimulants, sedatives, opiates, and hallucinogens/PCP, respondents were asked whether they had ever used each drug, their age at initiation, and whether they had used more than 5 times. Respondents who had used a drug more than 5 times were asked abuse and dependence questions based on DSM-III-R. Because of the low prevalence of illegal drug abuse in this sample, the illegal drug abuse/dependence diagnoses were combined. Alcohol dependence was also assessed using DSM-III-R criteria.

2.2.3. Covariates—Lifetime indices of psychiatric comorbidity, early regular alcohol and cigarette use, and Southeast Asia service were included as covariates in analyses. DSM-III-R depression (lifetime), conduct disorder (before age 16), and Post-Traumatic Stress Disorder (PTSD, lifetime) were assessed in the 1992 telephone diagnostic interview. Regular alcohol use was assessed in the 1992 telephone interview through a question that asked when they had “first had any wine, beer, or other alcohol at least once a month for 6 months or more”. The 25% of respondents (29% of regular drinkers) who indicated they began drinking on at least a monthly basis before age 18 were classified as early regular alcohol users, with those who never drank regularly coded as “no” for early regular alcohol use. Based on information from the 1987 self-report questionnaire, 66% of respondents had smoked 100+ cigarettes lifetime. Respondents were classified as early nicotine users if they reported smoking at least 100 cigarettes lifetime before age 18. Using this criterion, 28% of respondents were early regular smokers (46% of those who had smoked 100+ cigarettes lifetime). In the 1987 self-report questionnaire, respondents were asked whether they had been stationed in Southeast Asia during their Vietnam-era military service. Thirty-seven percent of the respondents served in Southeast Asia, 59% were stationed elsewhere, and 4% were of unknown status because of missing data in the 1987 questionnaire.

2.3. Analyses

The statistical package Mx (Neale, Boker, Xie, & Maes, 2003) was used for quantitative genetic modeling to determine the nature and extent of familial influences on early cannabis use and lifetime initiation. STATA (StataCorp, 1999) was used for conditional logistic regression analyses.

Twin pairs (n=3181 pairs) were classified into three groups: pairs concordant for early cannabis use (i.e., both used cannabis before age 18; 4%), pairs discordant for early cannabis use (i.e., one used cannabis before age 18 and the other did not; 9%), and pairs concordant for not using cannabis before age 18 (87%). Pairs discordant for early cannabis use were the focus of cotwin-control analyses using conditional logistic regression. In these analyses, twin pairs are matched for familial background and vary only in that one twin (considered to be the "case") is an early-user whereas the other twin (i.e., the "control") is not. The test is whether the "case" is at increased risk of having a particular outcome compared to the "control". Because the discordant cotwins of early users included both those who had never used cannabis (35%) and those who used cannabis later, two series of conditional logistic regression analyses were conducted: one examining both later-using and never-using cotwins (n=293), and one restricted to the subset of discordant pairs in which the cotwin initiated cannabis use later (n=190). These cotwin-control analyses permit the assessment of whether any associations are: a) attributable to an underlying familial liability, in which case one would expect early- and later/never- using twin members would be at equal risk for later problems, b) are causal (or due to a third unmeasured environmental risk factor), in which case the early-using twin would remain at greater risk for problems even after controlling for familial influences, or c) are influenced by both (a) and (b).

To test for potential zygosity differences in the association between early cannabis use and other substance use, we included in all initial analyses an interaction term between the respondent's zygosity and his early cannabis use status. As has been discussed in detail by others (Agrawal et al., 2004; Kendler et al., 1993), if this interaction term had been significant and there was an association between early cannabis use and later other substance use/abuse/dependence for dizygotic (DZ) twins only, this would have indicated that there were genetic influences that were contributing to the association between cannabis use and other drug use. This is the case because DZ twins share 50% of their segregating genes on average, thus it is possible that genetic influences not shared by the discordant twins could contribute to the association between early cannabis use and other drug use for DZ twins. In contrast, because monozygotic (MZ) twins share all of their genes, genes cannot contribute to twin pair discordance. Because all interaction terms failed to reach significance ($p > .10$), indicating no zygosity differences in the association between early cannabis use and other substance use, all analyses were collapsed across zygosity.

3. Results

3.1. Prevalence of illegal drug use

Table 1 shows the prevalence of drug use for all respondents and broken down into individuals from pairs concordant for early cannabis use, the early-users from discordant pairs, the later/never-users from discordant pairs, and individuals from pairs concordant for not using cannabis early. The percentages are consistent with a model in which level of early exposure to cannabis is a risk factor for other substance use: looking across the types of pairs, those pairs concordant for cannabis use before age 18 were the most likely to have tried other drugs, the early-users from the discordant pairs had slightly lower other drug use rates, the discordant cotwins of the early-users were next, and the individuals from pairs concordant for not using cannabis early were least likely to have tried other drugs. All four groups differed from each other significantly. That 65% of the non early-using twins from discordant twin pairs did use cannabis

later and only 38% of those individuals in pairs concordant for not using cannabis early tried cannabis later suggests some familial influence, either genetic or environmental. For regular alcohol use, the members of discordant pairs did not differ from each other, but all other group differences were significant.

3.2. Prevalence of drug abuse/dependence

Pairs concordant for not using cannabis early were at significantly reduced risk of drug abuse/dependence compared to all other groups (see Table 1). For 5 of the 8 drug abuse/dependence diagnoses, the pairs concordant for early cannabis use were at significantly increased risk compared to all other groups. Although the early-users from the discordant pairs had somewhat higher drug abuse/dependence rates than the later/never-users from discordant pairs, the differences were only significant for only 3 of the 8 drug abuse/dependence diagnoses.

3.3. Psychiatric and other substance use covariates

The rates of endorsement for the covariates are presented in Table 1. The percentage of respondents with no more than 12 years of education did not differ across the groups. Lifetime DSM-III-R depression was relatively consistent across groups, although individuals from pairs concordant for not using cannabis early had significantly lower rates than the other groups. There was evidence that early cannabis use was associated with other adolescent deviance (conduct disorder, early alcohol use, and early nicotine use). Southeast Asia service was relatively comparable across groups, but pairs concordant for not using cannabis early were significantly *more* likely to have served in Southeast Asia than members of the other groups. PTSD rates were lowest among the individuals in pairs concordant for not using cannabis early.

3.4. Familial influences on cannabis use

Quantitative genetic models indicated that both ever use of cannabis and early-onset cannabis use are influenced by genetic and environmental factors. In the full sample (3104 pairs with known zygosity), genetic (a^2=0.43 [0.26-0.60]) and shared environmental (c^2=0.25 [0.10-0.40]) influences together explained approximately 70% of the variance in lifetime cannabis use, with the remaining variance attributable to individual-specific factors (e^2=0.32 [0.27-0.37]). When examined at the population-level, early use showed a somewhat larger shared environment component (a^2=0.26 [0.03-0.52], c^2=0.49 [0.26-0.69], e^2=0.24 [0.18-0.31]). However, when restricted to pairs concordant for cannabis initiation (n=926 pairs with known zygosity of the 945 pairs concordant for ever use), familial influences on early cannabis use were primarily genetic (a^2=0.42 [0.09-0.78]), shared environmental influences were moderate but non-significant (c^2=0.33 [0.00-0.61]), and individual-specific factors explained the remaining 25% of the variance (e^2=0.25 [0.18-0.35]).

3.5. Discordance for early cannabis use

3.5.1. Early users vs. Later/Never users—In cotwin-control comparisons, the 293 respondents who used cannabis early were at significantly greater risk of trying other illegal drugs (see Table 2). In unadjusted models, early-users were 1.89-3.63 times more likely to have tried other substances. Furthermore, this risk was not attenuated when the models were adjusted for the covariates (OR: 2.71-4.09). Early cannabis use was also a significant predictor of any illegal drug abuse/dependence (but not cannabis abuse/dependence, or abuse/dependence for illegal substances other than cannabis). In models adjusted for covariates, early cannabis users were about 2.0 times more likely to have an illegal drug abuse/dependence diagnosis. Early cannabis users were also about 2.4 times more likely to be alcohol dependent than were their discordant cotwins (see Table 2).

3.5.2. Early-users vs. Later users—In the preceding analyses, some of the "control" twins used cannabis later whereas other "control" twins were abstainers. Table 3 compares the four subgroups of individuals from the two types of discordant pairs: early users from early-later discordant pairs, the later-using cotwin, early users from early-never discordant pairs, and the never-using cotwin. In general, there are few significant differences between the three groups of cannabis users, but all three have substantially higher rates of other drug use/abuse/dependence compared to the never-using cotwins. Analyses of the 190 pairs in which one twin used cannabis early and the other later indicated that, although early-using twins were at significantly greater risk of using sedatives, opiates, and hallucinogens, rates of illegal drug abuse/dependence and alcohol dependence were similar for the early- and later-using discordant twins (see Table 4). Although power to detect differences between early users and their discordant cotwins is reduced with the smaller sample size, the reduction in significance does not seem to be a function of power: the odds ratios in Table 4 are consistently considerably smaller than those in Table 2.

3.5.3. Discordance for cannabis use before age 17—Using a more stringent definition of early use (use prior to age 17) also did not alter the results. When the 176 early-using (before age 17) "cases" were compared to their later/never-using cotwins, the early users were at significantly increased risk of stimulant use, hallucinogen/PCP use, use of any illegal drug other than cannabis, and alcohol dependence (ORs: 2.18-3.30). Only alcohol dependence remained significant when the 130 early-users were compared to their later-using cotwins (OR=2.13).

4. Discussion

In this sample of Vietnam-era veteran twins, after controlling for familial influences and measured covariates, there was limited evidence that early-onset use conferred increased risk of other illegal drug use, drug abuse/dependence, and alcohol dependence compared to later-onset use. Although early cannabis use (before age 18) was associated with significantly increased risk for other drug use/abuse/dependence when comparing early-users to later/never-users, the association was dramatically reduced when early-users were compared to later users (excluding never-users). Compared to later/never users, early cannabis users were 2.7-4.1 times more likely to have used other illegal drugs, 1.5-2.1 times more likely to have illegal drug abuse/dependence, and 2.4 times more likely to have alcohol dependence. In contrast, when compared to later-users only (excluding never-users), early cannabis users were 1.3-2.5 times more likely to have tried other illegal drugs, 1.0-1.2 times more likely to have illegal drug abuse/dependence, and 1.3 times more likely to have alcohol dependence. Eight of the nine comparisons between early cannabis users and late/never users were significant, whereas only 3 of those comparisons remained significant when early-users were compared to later-users. Inclusion of psychiatric and other early substance use measures did not reduce the association between early cannabis use and other drug use and abuse/dependence.

Several researchers have reported that early substance use is a risk factor for substance abuse/dependence (Agrawal et al., 2006; Anthony & Petronis, 1995; Grant & Dawson, 1998; Wagner, Velasco-Mondragon, Herrera-Vasquez, Borges, & Lazcano-Ponce, 2005) even when using a cotwin-control design (Agrawal et al., 2004; Grant et al., 2006; Lessem et al., 2006; Lynskey et al., 2003, 2006) and, in two reports, even when early-users are compared to later users (Agrawal et al., 2004; Lynskey et al., 2003). Agrawal et al. (2004) reported smaller but still significant odds ratios when cannabis abstainers were removed from their analyses, but Lynskey et al.'s (2003) analyses suggested that the effect was comparable when early-users were compared to late/never-users and when they were compared to later-users. In our study the association with early-use was dramatically reduced when comparing early-users to later-users (versus later/never-users). Differences between our results and Lynskey et al.'s (2003)

could be related to sampling (e.g., country of residence, age, birth cohort, military service history, gender) and/or methodology (e.g., DSM-III-R vs. DSM-IV). Although Lynskey et al. (2003) found no evidence of gender differences and therefore collapsed their analyses across men and women, it is possible that they were able to do so because they had low power to detect gender differences. Because our analyses included men only, any undetected gender effect in their sample could have led to differences in the results of the two studies. In addition, our respondents were born approximately 15 years before those in the Lynskey et al. (2003) analysis and were about 12 years older at the time of interview, a difference that might be key since secular changes in the acceptability and availability of cannabis occurred between the times that the samples reached peak drug experimentation.

A number of explanations have been proposed for the observed association between early cannabis use and other drug use/abuse/dependence (Agrawal et al., 2007; Fergusson, Boden, & Horwood, 2006; Hall & Lynskey, 2005; Kandel, 2003a, 2003b). Although we are unable to test specific mechanisms with our data, a number of causal mechanisms could explain the association between early cannabis use and other substance use/abuse/dependence (Fergusson et al., 2006; Hall & Lynskey, 2005; Wagner & Anthony, 2002). Wagner and Anthony (2002) found support for an “exposure opportunity” process (individuals who use marijuana are more likely to have opportunities to use other illegal substances) as well as evidence that greater seeking of additional drug use opportunities could not entirely explain the increased access. Fergusson et al. (2006) also suggested that cannabis use could be causally linked with other drug use if it: 1) induces changes in brain chemistry, or 2) serves as a learning process for pleasurable effects of drugs. In fact, animal research has shown some support for changes in brain functioning as a result of substance exposures (Ellgren, Spano, & Hurd, 2007). Alternatively, the link between cannabis and other drug use and problems could stem from a general predisposition to drug use (or deviant behavior in general), such that the association is attributable to correlated vulnerabilities. Along this line, there is evidence, for both use and abuse/dependence, of moderate to substantial genetic overlap across illegal substances (Kendler et al., 2003, 2007; Tsuang et al., 1998). A third possibility is that both causal and correlated vulnerability mechanisms are involved in the association between cannabis use and other substance use/abuse/dependence. Agrawal et al. (2007) found support for the correlated vulnerabilities hypothesis, but could not rule out the possibility of causal influences as well. Our results are generally consistent with either: 1) a gateway model in which cannabis use, regardless of the age of initiation, increases risk, or 2) a correlated vulnerabilities model.

One potential criticism of the present analyses is our reliance on retrospective reports. Although prospective data would be preferable in many ways, the present data allow us to assess longer-term outcomes for events whose period of risk may extend well beyond substance initiation. To address potential concerns about our reliance on retrospective recall for age of initiation, we reran our analyses defining pairs as discordant only if they reported ages of initiation that differed by at least 2 years, and found no evidence that the pairs discordant by a short interval were driving the results observed in the original analyses (results available from the first author upon request). In addition, the present results are based on a sample of male Vietnam-era veterans who were predominantly Caucasian, and may not generalize to other ethnicities, to women, to non-veterans, or to cohorts who grew up in an era with different levels of acceptance of and/or access to cannabis.

In conclusion, the present analyses indicate that cannabis initiation, whether early or late, confers risk for other substance use/abuse/dependence that is independent of these familial influences. Given the lack of difference in risk for early- and later-users, the results are generally consistent with either a causal model, in which drug use results in developmental trajectory changes, or a correlated vulnerabilities model.

Acknowledgments

This study was supported by the Department of Veterans Affairs Health Services Research and Development Service and the Cooperative Studies Program (Study 992) and by NIH grants DA014632, DA014363, DA018660, DA018267 AA007728, AA011998.

The United States Department of Veterans Affairs has provided financial support for the development and maintenance of the Vietnam Era Twin (VET) Registry. Numerous organizations have provided invaluable assistance in the conduct of this study, including: Department of Defense; National Personnel Records Center, National Archives and Records Administration; the Internal Revenue Service; National Opinion Research Center; National Research Council, National Academy of Sciences; the Institute for Survey Research, Temple University. Most importantly, the authors gratefully acknowledge the continued cooperation and participation of the members of the VET Registry and their families. Without their contribution this research would not have been possible.

References

Agrawal A, Grant JD, Waldron M, Duncan AE, Scherrer JF, Lynskey MT, et al. Risk for initiation of substance use as a function of age of onset of cigarette, alcohol, and cannabis use: Findings in a Midwestern female twin cohort. Preventive Medicine 2006;43:125–128. [PubMed: 16697036]

Agrawal A, Lynskey MT, Bucholz KK, Martin NG, Madden PAF, Heath AC. Contrasting models of genetic co-morbidity for cannabis and other illicit drugs in adult Australian twins. Psychological Medicine 2007;37:49–60. [PubMed: 17076916]

Agrawal A, Neale MC, Prescott CA, Kendler KS. A twin study of early cannabis use and subsequent use and abuse/dependence of other illicit drugs. Psychological Medicine 2004;34:1227–1237. [PubMed: 15697049]

Anthony JC, Petronis KR. Early-onset drug use and risk of later drug problems. Drug and Alcohol Dependence 1995;40:9–15. [PubMed: 8746919]

Donovan JE, Jessor R. Structure of problem behavior in adolescence and young adulthood. Journal of Consulting and Clinical Psychology 1985;53:890–904. [PubMed: 4086689]

Eisen S, Neuman R, Goldberg J, Rice J, True W. Determining zygosity in the Vietnam era twin registry: An approach using questionnaires. Clinical Genetics 1989;35:423–432. [PubMed: 2736790]

Eisen S, True W, Goldberg J, Henderson W, Robinette CD. The Vietnam era Twin (VET) registry: Method of construction. Acta Geneticae Medicae et Gemellologiae 1987;36:61–66. [PubMed: 3673478]

Ellgren M, Spano SM, Hurd YL. Adolescent cannabis exposure alters opiate intake and opioid limbic neuronal populations in adult rats. Neuropsychopharmacology 2007;32:607–615. [PubMed: 16823391]

Fergusson DM, Boden JM, Horwood LJ. Cannabis use and other illicit drug use: testing the cannabis gateway hypothesis. Addiction 2006;101:556–569. [PubMed: 16548935]

Fu Q, Heath AC, Bucholz KK, Nelson E, Goldberg J, Lyons MJ, et al. Shared genetic risk of major depression, alcohol dependence, and marijuana dependence: Contribution of antisocial personality disorder in men. Archives of General Psychiatry 2002;59:1125–1132. [PubMed: 12470129]

Grant BF, Dawson DA. Age of onset of drug use and its association with DSM-IV drug abuse and dependence: Results from the National Longitudinal Alcohol Epidemiologic Survey. Journal of Substance Abuse 1998;10:163–173. [PubMed: 9854701]

Grant JD, Scherrer JF, Lynskey MT, Lyons MJ, Eisen SA, Tsuang MT, et al. Adolescent alcohol use is a risk factor for adult alcohol and drug dependence: Evidence from a twin design. Psychological Medicine 2006;36:109–118. [PubMed: 16194286]

Hall WD, Lynskey M. Is cannabis a gateway drug? Testing hypotheses about the relationship between cannabis use and the use of other illicit drugs. Drug and Alcohol Review 2005;24:39–48. [PubMed: 16191720]

Hammer T, Vaglum P. Use of alcohol and drugs in the transitional phase from adolescence to young adulthood. Journal of Adolescence 1990;13:129–142. [PubMed: 2387916]

Henderson WG, Eisen S, Goldberg J, True WR, Barnes JE, Vitek ME. The Vietnam Era Twin Registry: A resource for medical research. Public Health Reports 1990;105:368–373. [PubMed: 2116638]

Jessor R, Chase JA, Donovan JE. Psychosocial correlates of marijuana use and problem drinking in a national sample of adolescents. American Journal of Public Health 1980;70:604–610. [PubMed: 7377436]

Johnston, LD.; O'Malley, PM.; Bachman, JG. Monitoring the Future national survey results on drug use. National Institute on Drug Abuse; Bethesda, MD: 2003. p. 1975-2002.

Kandel DB. Does marijuana use cause the use of other drugs? Journal of the American Medical Association 2003a;289:482–483. [PubMed: 12533129]

Kandel, DB., editor. Stages and pathways of drug involvement: Examining the gateway hypothesis. Cambridge University Press; New York: 2003b.

Kandel DB, Davies M, Karus D, Yamaguchi K. The consequences in young adulthood of adolescent drug involvement: An overview. Archives of General Psychiatry 1986;43:746–754. [PubMed: 3729669]

Kandel DB, Yamaguchi K, Chen K. Stages of progression in drug involvement from adolescence to adulthood: Further evidence for the gateway theory. Journal of Studies on Alcohol 1992;53:447–457. [PubMed: 1405637]

Kendler KS, Jacobson KC, Prescott CA, Neale MC. Specificity of genetic and environmental risk factors for use and abuse/dependence of cannabis, cocaine, hallucinogens, sedatives, stimulants, and opiates in male twins. American Journal of Psychiatry 2003;160:687–695. [PubMed: 12668357]

Kendler KS, Karkowski LM, Neale MC, Prescott CA. Illicit psychoactive substance use, heavy use, abuse, and dependence in a US population-based sample of male twins. Archives of General Psychiatry 2000;57:261–269. [PubMed: 10711912]

Kendler KS, Myers J, Prescott CA. Specificity of genetic and environmental risk factors for symptoms of cannabis, cocaine, alcohol, caffeine, and nicotine dependence. Archives of General Psychiatry 2007;64:1313–1320. [PubMed: 17984400]

Kendler KS, Neale MC, MacLean CJ, Heath AC, Eaves LJ, Kessler RC. Smoking and major depression: A causal analysis. Archives of General Psychiatry 1993;50:36–43. [PubMed: 8422220]

Lessem JM, Hopfer CJ, Haberstick BC, Timberlake D, Ehringer MA, Smolen A, et al. Relationship between adolescent marijuana use and young adult illicit drug use. Behavior Genetics 2006;36:498–506. [PubMed: 16565887]

Lynskey MT, Heath AC, Bucholz KK, Slutske WS, Madden PAF, Nelson EC, et al. Escalation of drug use in early-onset cannabis users vs. co-twin controls. Journal of the American Medical Association 2003;289:427–433. [PubMed: 12533121]

Lynskey MT, Heath AC, Nelson EC, Bucholz KK, Madden PAF, Slutske WS, et al. Genetic and environmental contributions to cannabis dependence in a national young adult twin sample. Psychological Medicine 2002;32:195–207. [PubMed: 11871371]

Lynskey MT, Vink JM, Boomsma DI. Early onset cannabis use and progression to other drug use in a sample of Dutch twins. Behavior Genetics 2006;36:195–200. [PubMed: 16402286]

Maes HH, Woodard CE, Murrelle L, Meyer JM, Silberg JL, Hewitt JK, et al. Tobacco, alcohol and drug use in eight- to sixteen-year-old twins: The Virginia Twin Study of Adolescent Behavioral Development. Journal of Studies on Alcohol 1999;60:293–305. [PubMed: 10371255]

Morral AR, McCaffrey DF, Paddock SM. Reassessing the marijuana gateway effect. Addiction 2002;97:1493–1504. [PubMed: 12472629]

Neale, MC.; Boker, SM.; Xie, G.; Maes, HH. Mx: Statistical modeling. Vol. 6th ed.. VCU Box 900126, Department of Psychiatry; Richmond, VA: 2003.

Pedersen W, Skrondal A. Alcohol consumption debut: Predictors and consequences. Journal of Studies on Alcohol 1998;59:32–42. [PubMed: 9498313]

Rhee SH, Hewitt JK, Young SE, Corley RP, Crowley TJ, Stallings MC. Genetic and environmental influences on substance initiation, use, and problem use in adolescents. Archives of General Psychiatry 2003;60:1256–1264. [PubMed: 14662558]

Robins, LN.; Helzer, JE.; Cottler, L.; Goldring, E. NIMH Diagnostic Interview Schedule. Version III—Revised (DIS-III-R). Washington University School of Medicine, Department of Psychiatry; St. Louis, MO: 1989.

StataCorp. Stata Statistical Software: Release 6.0. Stata Corp.; College Station, TX: 1999.

True WR, Heath AC, Scherrer JF, Xian H, Lin N, Eisen SA, et al. Interrelationship of genetic and environmental influences on conduct disorder and alcohol and marijuana dependence symptoms. American Journal of Medical Genetics 1999;88:391–397. [PubMed: 10402507]

Tsuang MT, Lyons MJ, Eisen SA, Goldberg J, True W, Lin N, et al. Genetic influences on DSM-III-R drug abuse and dependence: A study of 3,372 twin pairs. American Journal of Medical Genetics 1996;67:473–477. [PubMed: 8886164]

Tsuang MT, Lyons MJ, Harley RM, Xian H, Eisen S, Goldberg J, et al. Genetic and environmental influences on transitions in drug use. Behavior Genetics 1999;29:473–479. [PubMed: 10857252]

Tsuang MT, Lyons MJ, Meyer JM, Doyle T, Eisen SA, Goldberg J, et al. Cooccurrence of abuse of different drugs in men: The role of drug-specific and shared vulnerabilities. Archives of General Psychiatry 1998;55:967–972. [PubMed: 9819064]

Wagner FA, Anthony JC. Into the world of illegal drug use: Exposure opportunity and other mechanisms linking the use of alcohol, tobacco, marijuana, and cocaine. American Journal of Epidemiology 2002;155:918–925. [PubMed: 11994231]

Wagner FA, Velasco-Mondragon HE, Herrera-Vasquez M, Borges G, Lazcano-Ponce E. Early alcohol or tobacco onset and transition to other drug use among students in the State of Morelos, Mexico. Drug and Alcohol Dependence 2005;77:93–96. [PubMed: 15607846]

Xian H, Scherrer JF, Grant JD, Eisen SA, True WR, Jacob T, et al. Genetic and environmental contributions to nicotine, alcohol, and cannabis dependence in male twins. Addiction 2008;103:1391–1398. [PubMed: 18855830]

Addict Behav. Author manuscript; available in PMC 2011 January 1.

Table 1

Prevalence (%) of lifetime drug use and abuse/dependence, early licit substance use, and psychiatric diagnoses for: the whole sample, individuals from twin pairs where both twins reported early onset cannabis use; early cannabis users from twin pairs discordant for early use; later/never cannabis users from discordant pairs and individuals from twin pairs concordant for not using cannabis before age 18.

	All men (n=6362)	Indiv. in prs. conc. for early use (n=246)	Early users from disc. pairs (n=293)	Later/Never users from disc. pairs (n=293)	Indiv. in prs conc. for no early use (n=5530)
Substance Use					
Cannabis	44.4	100.0[a]	100.0[a]	64.9[b]	37.9[c]
Stimulants/Cocaine	20.2	77.6[a]	62.5[b]	37.9[c]	14.4[d]
Sedatives	10.7	49.6[a]	35.5[b]	21.2[c]	7.1[d]
Opiates	6.5	37.4[a]	23.6[b]	15.4[c]	3.8[d]
Hallucinogens/PCP	11.8	59.4[a]	42.7[b]	24.6[c]	7.4[d]
Any non-cannabis	22.5	80.9[a]	67.9[b]	41.0[c]	16.5[d]
Regular alcohol use	87.7	98.4[a]	94.9[b]	93.5[b]	86.5[c]
Substance Abuse/Dependence*					
Cannabis	6.5	30.5[a]	18.4[b]	15.0[b]	4.3[c]
Stimulants/Cocaine	3.8	22.4[a]	10.9[b]	10.2[b]	2.3[c]
Sedatives	1.2	9.8[a]	4.1[a]	1.0[b]	0.7[b]
Opiates	1.0	6.5[a]	4.8[a]	2.4[a]	0.5[b]
Hallucinogens/PCP	0.9	9.4[a]	2.4[b]	1.7[b]	0.5[c]
Any Illegal	9.0	43.9[a]	27.7[b]	20.5[c]	5.9[d]
Any non-cannabis	5.0	29.7[a]	16.7[b]	12.3[b]	2.9[c]
Alcohol Dep.	32.3	62.6[a]	56.7[a]	37.9[b]	29.3[c]
Covariates					
Education ≤ 12 yrs.	34.1	37.6	37.1	36.6	33.7
Depression (lifetime)	8.7	16.4[a]	13.0[a]	12.7[a]	7.9[b]
Conduct disorder	8.2	32.8[a]	21.9[b]	14.7[c]	6.1[d]
Early alcohol use	25.1	62.6[a]	57.7[a]	39.9[b]	20.9[c]

	All men (n=6362)	Indiv. in prs. conc. for early use (n=246)	Early users from disc. pairs (n=293)	Later/Never users from disc. pairs (n=293)	Indiv. in prs conc. for no early use (n=5530)
Early nicotine use	31.1	67.1[a]	64.5[a]	48.2[b]	26.8[c]
Southeast Asia service	38.6	22.9[a]	30.9[a]	30.7[a]	40.0[b]
PTSD lifetime	9.0	17.9[a]	11.7[b]	14.0[a,b]	8.2[c]

Differing superscript letters indicate that the prevalences are significantly different ($p < .05$)

*Population prevalence for abuse/dependence measures

Table 2

Lifetime illegal drug use and substance abuse/ dependence in twin pairs discordant for cannabis use before age 18 (n = 293 pairs)

Outcome	Unadjusted Conditional Odds ratio	Adjusted Conditional Odds ratio	Covariates
Use			
Stimulants/Cocaine	**3.25* (2.18 – 4.84)**	**3.55* (2.21 – 5.72)**	CD*, DEPRt
Sedatives	**2.83* (1.75 – 4.56)**	**3.57* (1.82 – 6.99)**	CD*, ENIC*, EDUCt, PTSDt
Opiates	**1.89* (1.18 – 3.02)**	**2.71* (1.36 – 5.39)**	SEA*, PTSD*, EALCt
Hallucinogens/PCP	**3.12* (1.98 – 4.91)**	**4.09* (2.28 – 7.31)**	PTSD*
Any non-cannabis illegal	**3.63* (2.42 – 5.45)**	**3.57* (2.27 – 5.61)**	CDt
Abuse/Dependence			
Cannabis	1.40 (0.83 – 2.35)	1.49 (0.76 – 2.92)	SEA*, PTSDt
Any non-cannabis illegal	1.48 (0.91 – 2.42)	**2.13* (1.14 – 3.96)**	PTSD*, EDUCt
Any illegal drug	**1.66* (1.07 – 2.58)**	**2.02* (1.18 – 3.45)**	PTSD*
Alcohol dependence	**2.41* (1.66 – 3.51)**	**2.36* (1.53 – 3.63)**	PTSD*

* indicates $p < .05$; t indicates $p < .10$; EDUC= 12 years of education or less, DEPR=depression, CD=conduct disorder, EALC=early alcohol use, ENIC=early nicotine use, SEA=Southeast Asia service, PTSD=post-traumatic stress disorder

Table 3

Comparison of lifetime drug use and abuse/dependence, early licit substance use, and psychiatric diagnoses for early cannabis-use for early-later use and early-never use discordant pairs.

	Early-Later Discordant Pairs		Early-Never Discordant Pairs	
	Early users (n=190)	**Later-users (n=190)**	**Early users (n=103)**	**Never-users (n=103)**
Substance Use				
Cannabis	100[a]	100[a]	100[a]	0[b]
Stimulants/Cocaine	63.2[a]	58.4[a]	61.2[a]	0[b]
Sedatives	41.1[a]	32.6[b]	25.2[b]	0[c]
Opiates	27.9[a]	23.7[a,b]	15.5[b]	0[c]
Hallucinogens/PCP	46.3[a]	37.9[b]	35.9[a,b]	0[c]
Any non-cannabis	69.5[a]	63.2[a]	65.1[a]	0[b]
Regular alcohol use	93.7[a,b]	96.8[a]	97.1[a]	87.4[b]
Substance Abuse/Dependence				
Cannabis	20.5[a]	23.2[a]	14.6[a]	0[b]
Stimulants/Cocaine	10.5[a]	15.8[a]	11.7[a]	0[b]
Sedatives	4.2[a]	1.6[a]	3.9[a]	0[a]
Opiates	6.8[a]	3.7[a,b]	1.0[b]	0[b]
Hallucinogens/PCP	3.2[a]	2.6[a]	1.0[a]	0[a]
Any Illegal	30.0[a]	31.6[a]	23.3[a]	0[b]
Any non-cannabis	18.4[a]	19.0[a]	13.6[a]	0[b]
Alcohol Dep.	54.2[a,b]	45.3[a]	61.2[b]	24.3[c]
Covariates				
Education ≤ 12 yrs.	38.8[a]	36.8[a]	34.0[a]	36.1[a]
Depression (lifetime)	15.9[a]	14.2[a]	7.8[a]	9.8[a]
Conduct disorder	20.6[a]	15.8[a,b]	24.3[a]	12.8[b]
Early alcohol use	61.1[a]	41.1[b,c]	51.5[a,b]	37.9[c]
Early nicotine use	63.7[a]	51.7[b]	65.9[a]	41.7[b]
Southeast Asia service	30.9[a]	32.8[b,c]	30.9[a,b]	26.8[c]
PTSD lifetime	12.2[a,b]	17.4[b]	10.8[a,b]	7.8[a]

Differing superscript letters indicate that the prevalences are significantly different ($p < .05$)

*Population prevalence for abuse/dependence measures

Table 4

Lifetime illegal drug use and substance abuse/ dependence in twin pairs discordant for cannabis use before age 18 years with sample restricted to those concordant for lifetime cannabis use (N = 190 pairs)

Outcome	Unadjusted Conditional Odds ratio	Adjusted Conditional Odds ratio	Covariates
Use			
Stimulants/Cocaine	1.28 (0.80 – 2.04)	1.28 (0.80 – 2.04)	---
Sedatives	**1.70* (1.01 – 2.85)**	**2.53* (1.19 – 5.36)**	ENIC*, CD*, EDUC*, PTSDt
Opiates	1.30 (0.78 – 2.15)	**2.33* (1.14 – 4.74)**	SEA*, PTSD*
Hallucinogens/PCP	1.64 (0.99 – 2.71)	**2.13* (1.10 – 4.14)**	PTSD*, EALCt
Any non-cannabis illegal	1.40 (0.87 – 2.24)	1.40 (0.87 – 2.24)	---
Abuse/Dependence			
Cannabis	0.80 (0.44 – 1.45)	0.96 (0.47 – 1.99)	SEA*
Any non-cannabis illegal	0.96 (0.56 – 1.66)	1.17 (0.55 – 2.51)	PTSD*, EDUC*, EALCt
Any illegal drug	0.91 (0.55 – 1.50)	1.20 (0.66 – 2.19)	PTSD*
Alcohol dependence	1.52 (0.97 – 2.36)	1.30 (0.77 – 2.20)	ENICt, PTSDt

* indicates $p < .05$; t indicates $p < .10$; EDUC= 12 years of education or less, DEPR=depression, CD=conduct disorder, EALC=early alcohol use, ENIC=early nicotine use, SEA=Southeast Asia service, PTSD=post-traumatic stress disorder