

Escalation of Drug Use in Early-Onset Cannabis Users vs Co-twin Controls

Michael T. Lynskey, PhD

Andrew C. Heath, DPhil

Kathleen K. Bucholz, PhD

Wendy S. Slutske, PhD

Pamela A. F. Madden, PhD

Elliot C. Nelson, MD

Dixie J. Statham, MA

Nicholas G. Martin, PhD

OVER THE PAST DECADE there has been a steady increase both in the prevalence of cannabis (marijuana) use among young people^{1,2} and in the number of people entering treatment for cannabis-related problems.³ In 1999 there were 220 000 cannabis-related admissions to publicly funded substance abuse treatment programs in the United States.³ This represented 14% of all such treatment admissions, with admissions occurring primarily among youth: approximately a third of all cannabis-related admissions were among people 12 to 17 years of age and a further third were among those 18 to 25 years of age. These increases in treatment seeking have been paralleled by heightened concerns about the long-term consequences of chronic cannabis use^{4,5} and a recognition of the need for treatment and other interventions to ameliorate the effects of drug dependence, which is best characterized as a chronic, recurring condition.⁶

The majority of cannabis-related admissions among youth result from referrals either from the justice or educational systems,⁷ and it is probable that at least some of these referrals were mo-

Context Previous studies have reported that early initiation of cannabis (marijuana) use is a significant risk factor for other drug use and drug-related problems.

Objective To examine whether the association between early cannabis use and subsequent progression to use of other drugs and drug abuse/dependence persists after controlling for genetic and shared environmental influences.

Design Cross-sectional survey conducted in 1996-2000 among an Australian national volunteer sample of 311 young adult (median age, 30 years) monozygotic and dizygotic same-sex twin pairs discordant for early cannabis use (before age 17 years).

Main Outcome Measures Self-reported subsequent nonmedical use of prescription sedatives, hallucinogens, cocaine/other stimulants, and opioids; abuse or dependence on these drugs (including cannabis abuse/dependence); and alcohol dependence.

Results Individuals who used cannabis by age 17 years had odds of other drug use, alcohol dependence, and drug abuse/dependence that were 2.1 to 5.2 times higher than those of their co-twin, who did not use cannabis before age 17 years. Controlling for known risk factors (early-onset alcohol or tobacco use, parental conflict/separation, childhood sexual abuse, conduct disorder, major depression, and social anxiety) had only negligible effects on these results. These associations did not differ significantly between monozygotic and dizygotic twins.

Conclusions Associations between early cannabis use and later drug use and abuse/dependence cannot solely be explained by common predisposing genetic or shared environmental factors. The association may arise from the effects of the peer and social context within which cannabis is used and obtained. In particular, early access to and use of cannabis may reduce perceived barriers against the use of other illegal drugs and provide access to these drugs.

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tivated more by concern over the future consequences of early initiation to cannabis use than by apparent negative effects of current cannabis use. A major focus of concern is the extent to which early cannabis use may increase the risks for escalation to other drug use and drug dependence. Stage theory posits that there is an invariant sequence in initiation and use of drugs, with use of cannabis preceding the use of "hard" drugs such as cocaine and heroin.⁸⁻¹⁰ This theory has been highly influential in drug policy debates and has provided a major rationale for sustaining prohibition against cannabis,¹¹ as it is assumed that delaying or

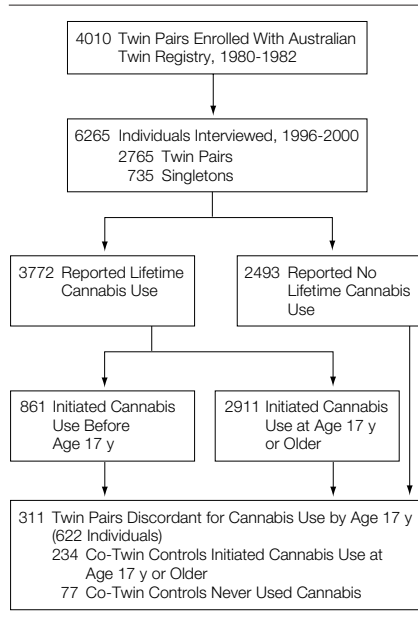
preventing early cannabis use may reduce risks of other illicit drug use.

While this broad theory has found some empirical support,^{8-10,12-14} such data on temporal sequencing do not establish that the use of one drug *causes* the

Author Affiliations: Queensland Institute of Medical Research, Brisbane, Queensland, Australia (Drs Lynskey and Martin and Ms Statham); Missouri Alcoholism Research Center and Department of Psychiatry, Washington University School of Medicine, St Louis (Drs Lynskey, Heath, Bucholz, Madden, and Nelson); and Missouri Alcoholism Research Center and Department of Psychology, University of Missouri, Columbia (Dr Slutske).

Corresponding Author and Reprints: Michael T. Lynskey, PhD, Missouri Alcoholism Research Center, Department of Psychiatry, Washington University School of Medicine, 40 N Kingshighway, Suite One, St Louis, MO 63108 (e-mail: mlynskey@matlock.wustl.edu).

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Figure. Sample Size and Sample Selection Criteria

use of drugs higher up the sequence.^{11,14} Rather, the observed pattern of initiation and use may reflect other factors such as availability and access.¹¹ Nonetheless, several studies using event history analysis¹⁵ and regression analyses¹⁶⁻¹⁹ have reported that early initiation to cannabis use remains a significant risk factor for both the use of other drugs and experiencing drug-related problems.

We are unaware of any studies that have controlled for genetic influences on the association between earlier initiation of cannabis use and other drug use and drug-related problems. Nonetheless, one viable hypothesis to explain this apparent association is that it arises from the joint influence of genetic and/or shared environmental factors on both risks of early initiation to cannabis use and, independently of this, on increased risks of subsequent drug use and dependence. This hypothesis is supported by evidence that cannabis and other drug use and drug abuse/dependence are moderately to highly heritable.²⁰⁻²²

The examination of other drug use and drug abuse/dependence in twin pairs discordant for early cannabis use provides a powerful test of the hypoth-

esis that the association between early cannabis use and later outcomes can be explained by common predisposing genetic and/or shared environmental risk factors. Since these predisposing factors are shared by twin pairs raised together, if the association between early cannabis use and later drug use can be explained by shared environmental factors, then in twin pairs discordant for early cannabis use, individuals who do not initiate early cannabis use should be at equal risk of developing drug-related problems as their co-twin who initiates cannabis use early. If correlated genetic effects explain these associations, then monozygotic pairs discordant for early use should still have equal risks. In contrast, if the association is causal or explained by environmental factors for which twin pairs are discordant, we would expect to find higher rates of other drug use and abuse/dependence in the early cannabis user than in his or her co-twin. In this article, this issue is explored using data from a large community sample of young adult Australian monozygotic and dizygotic twins.

METHODS

Interviewees were members of the young adult cohort of the Australian Twin Register, a volunteer twin panel born between 1964-1971.^{20,23,24} The data presented in this report are derived from responses to a single telephone interview during the period 1996-2000 when the median age of the sample was 30 years (range, 24-36 years). Informed consent was obtained from participants prior to administering the interviews, as approved by the institutional review boards of Washington University School of Medicine and the Queensland Institute of Medical Research.

An overview of the study design is shown in the FIGURE. Of 4010 pairs that could be traced, interviews were completed with both members of 2765 pairs (69% pair-wise response rate) and 1 member of another 735 pairs (78% individual response rate). A total of 861 members of the sample (13.7%) reported initiating cannabis use before age 17

years; 311 of these (36.1%) were from same-sex twin pairs in which their co-twin had not used cannabis by age 17 years. The analyses in this article are based on this subset of 622 same-sex twins from pairs discordant for early cannabis use. There were 74 female and 62 male monozygotic twin pairs and 84 female and 91 male same-sex dizygotic twin pairs. Zygosity was determined on the basis of responses to standard questions about physical similarity and confusion of the twins by parents, teachers, and strangers, methods that have been found to give better than 95% agreement with results of genotyping.²⁵⁻²⁸

Assessments

A structured diagnostic interview designed for genetic studies on alcoholism, the Semi-Structured Assessment for the Genetics of Alcoholism,²⁹ was adapted for telephone use with an Australian sample and updated for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* diagnostic criteria.³⁰ The interview also included assessments of sociodemographic factors, childhood family environment, and experiencing childhood sexual abuse.²³ These measures are described below.

Measures of Subsequent Drug Involvement

Lifetime Drug Use. Respondents were asked whether they had ever engaged in nonmedical use of other drugs. In the analysis sample of 622 individuals from same-sex pairs discordant for early cannabis use, the following results were found: (1) sedative use (ie, benzodiazepines, barbiturates) was reported by 12.7% of women and 14.8% of men; (2) hallucinogen use was reported by 18.7% of women and 35.2% of men; (3) cocaine or other stimulant use was reported by 32.4% of women and 42.4% of men; and (4) opioid use was reported by 6.7% of women and 13.5% of men.

Lifetime Drug Abuse/Dependence. Individuals reporting using cannabis, sedatives, cocaine/other stimulants, or opioids on at least a monthly basis were asked additional questions concern-

Table 1. Men, Women, and the Total Sample of Discordant Twins Who Met Criteria for Drug Abuse and Dependence*

Drug	Men (n = 306)			Women (n = 316)			Total (N = 622)		
	Abuse	Dependence	Abuse/ Dependence	Abuse	Dependence	Abuse/ Dependence	Abuse	Dependence	Abuse/ Dependence
Cannabis	57 (18.6)	96 (31.4)	153 (50.0)	23 (7.3)	65 (20.6)	88 (27.9)	80 (12.9)	161 (25.9)	241 (38.7)
Sedatives	2 (0.7)	4 (1.3)	6 (2.0)	...	5 (1.6)	5 (1.6)	2 (0.3)	9 (1.5)	11 (1.8)
Cocaine/stimulants	13 (4.2)	23 (7.5)	36 (11.8)	4 (1.3)	13 (4.1)	17 (5.4)	17 (2.7)	36 (5.8)	53 (8.5)
Opioids	2 (0.7)	6 (2.0)	8 (2.6)	...	6 (1.9)	6 (1.9)	2 (0.3)	12 (1.9)	14 (2.3)
Any illicit drug	56 (18.3)	101 (33.0)	157 (51.3)	22 (7.0)	71 (22.5)	93 (29.4)	78 (12.5)	172 (27.7)	250 (40.2)
Alcohol	...	137 (44.8)	88 (27.9)	225 (36.2)	...

*Data are presented as No. (%). Ellipses indicate not applicable.

ing the extent to which they may have experienced symptoms of drug abuse (use in physically hazardous situations; use interfering with major role obligations) or dependence (using more frequently or for longer periods than intended; needing larger amounts to achieve an effect [tolerance]; continued use despite use causing emotional problems; recurrent desire to cut down on use). Abuse was operationalized by endorsement of either abuse symptom; dependence was operationalized by endorsement of 2 or more dependence symptoms. While the dependence measure did not provide formal *DSM-IV* criteria, previous analyses exploring the validity of these modified criteria for cannabis dependence indicated that they had both excellent sensitivity (96.7%) and specificity (94.6%) when compared with *DSM-IV* criteria.²⁰

Given the relatively low prevalence of drug abuse and dependence, measures of abuse and dependence for each drug class were combined. We assessed abuse/dependence for the following drug classes: (1) cannabis; (2) sedatives (ie, benzodiazepines, barbiturates); (3) cocaine/other stimulants; and (4) opioids. Additionally, these drug classes were combined to form a measure of any drug abuse or dependence. The prevalence of these outcomes is summarized separately by sex in TABLE 1.

Lifetime Alcohol Dependence. Lifetime alcohol dependence was assessed using full *DSM-IV*³⁰ criteria: 27.9% of women and 44.8% of men met criteria for alcohol dependence.

Family, Social, and Individual Factors

A number of family, social, and individual factors were included in the analysis as control variables. These were selected on the basis of a previous analysis with this sample that identified risk factors associated with cannabis dependence.²⁰

Psychiatric Disorders. Criteria for conduct disorder and major depression from the *DSM-IV*³⁰ were assessed using the modified Semi-Structured Assessment for the Genetics of Alcoholism, and diagnoses were assigned by computer algorithm. A nondiagnostic measure of social anxiety was also defined.²³

Early Tobacco Use. A measure of early tobacco use was constructed by classifying subjects who reported smoking at least 1 day a week for a period of 3 weeks or more before age 17 years as early tobacco users (36.6% of twins from pairs discordant for early cannabis use reported such use).

Early Regular Alcohol Use. A measure of early alcohol use was constructed by classifying subjects who reported that they started drinking alcohol at least once a month for a period of 6 months or more before age 17 years as early regular alcohol drinkers (11.6% of twins from pairs discordant for early cannabis use reported such use).

Statistical Analyses

All statistical analyses were conducted using SAS³¹ and STATA.³² As an initial test of heritability of onset of cannabis use, rates of concordance for early (before age 17 years) cannabis use were

compared between monozygotic and dizygotic twin pairs. Differences in concordance rates were tested using the Breslow-Day test of heterogeneity of odds ratios (ORs), and separate tests were conducted for males and females. Conditional logistic regression models were then fitted to test for excess risk to early-onset cannabis users from same-sex discordant pairs, compared with their co-twin controls. The significance of the interactions between early cannabis use and both twin pair zygosity and sex were tested and, as these were nonsignificant ($P > .10$ in all cases), data were pooled across zygosity and sex. Analyses were repeated including the family and individual control variables described above. Stepwise regression with backward selection was conducted with the measure of early cannabis use forced into the model. These analyses were used to estimate conditional ORs for drug use and drug abuse/dependence in twins discordant for early cannabis use with control for other significant predictors.

Power was estimated using computer simulation. For example, for cocaine/stimulant abuse or dependence, we first obtained estimates of the prevalence ($p_E = 12.5\%$, exposed twin; $p_U = 4.5\%$, unexposed co-twin) and of the twin-pair tetrachoric correlation ($r = 0.47$). We then estimated the minimum $OR = p_E(1 - p_E)/p_U(1 - p_U)$, such that a difference between the prevalence in the exposed twin and the unexposed co-twin would be detected with 80% power given a sample of 311 twin pairs at the .01 significance level, with

Table 2. Drug Use Outcomes in Twin Pairs Discordant for Cannabis Use Before Age 17 Years (N = 311 Pairs)

	Lifetime Prevalence		Unadjusted Conditional OR (95% CI)	Conditional OR Adjusted for Covariates	
	Early Cannabis Users, No. (%)	Co-twins, No. (%)		OR (95% CI)	Significant Covariates*
Use					
Sedatives	59 (19.0)	26 (8.4)	2.83 (1.66-4.85)	2.28 (1.20-4.31)	1, 3, 4
Hallucinogens	110 (35.4)	56 (18.0)	5.15 (2.85-9.33)	5.15 (2.85-9.33)	...
Cocaine/stimulants	149 (47.9)	82 (26.4)	4.19 (2.60-6.75)	4.06 (2.30-7.17)	1, 2, 4
Opioids	42 (13.5)	20 (6.4)	2.57 (1.39-4.77)	2.34 (1.13-4.85)	4
Illicit drug abuse/dependence					
Cannabis	142 (45.7)	99 (31.8)	2.13 (1.45-3.13)	1.96 (1.25-3.09)	1, 2, 5
Sedatives	8 (2.6)	3 (1.0)	2.67 (0.71-10.05)	2.67 (0.71-10.05)	...
Cocaine/stimulants	39 (12.5)	14 (4.5)	4.13 (1.91-8.93)	3.98 (1.73-9.17)	3
Opioids	11 (3.5)	3 (1.0)	3.67 (1.02-13.14)	3.67 (1.02-13.14)	...
Any illicit drug abuse/dependence	148 (47.6)	102 (32.8)	2.24 (1.52-3.30)	1.98 (1.26-3.10)	1, 2, 5
Alcohol dependence	133 (42.8)	92 (29.6)	2.17 (1.46-3.24)	1.85 (1.21-2.83)	3, 4

Abbreviations: CI, confidence interval; OR, odds ratio.
 *For significant covariates, 1 indicates early (before age 17 years) regular use of tobacco; 2, early (before age 17 years) regular use of alcohol; 3, conduct disorder; 4, major depression; and 5, social anxiety. Ellipses indicate that there were no significant covariates for the outcome.

p_U and r fixed at their observed values. Our results indicate that power would be 80% or better for an OR greater than 1.7 for 5 measures: hallucinogen use, cocaine/stimulant use, cannabis abuse/dependence, any abuse or dependence, and alcohol dependence. Power was over 80% for an OR greater than 2.5 for the measures sedative use, opioid use, and cocaine/stimulant abuse or dependence. Power was low under the reasonable range of OR for the measures sedative abuse/dependence and opioid abuse/dependence.

RESULTS

Rates of concordance for early cannabis use (before age 17 years) among the full interview sample (2765 pairs; see Figure) were significantly higher in monozygotic than dizygotic twin pairs for both men (65 concordant and 88 discordant monozygotic pairs vs 59 concordant and 110 discordant dizygotic pairs, $\chi^2_1=7.92, P=.005$) and women (61 concordant and 98 discordant monozygotic pairs vs 44 concordant and 111 discordant dizygotic pairs, $\chi^2_1=7.80, P=.005$), indicating heritable influences on age of initiation of cannabis use. The first 2 columns of TABLE 2 show estimates of the lifetime prevalence of drug use and drug abuse/dependence for those initiating cannabis use before age 17 years and for their

co-twins (who either reported no lifetime cannabis use or who reported initiating cannabis use at age 17 years or older). The majority of subjects reporting both cannabis and other illicit drug use reported initiating cannabis use before initiating the use of other drugs. Three individuals reported initiating sedative use before cannabis use, 6 individuals initiated hallucinogen use, 5 initiated stimulant use, and 3 initiated opioid use before the use of cannabis. These individuals were excluded from the analyses. Table 2 also shows the conditional ORs, both unadjusted and adjusted for major risk factors, for the drug use outcomes. The results in Table 2 can be summarized as follows:

1. Relative to their co-twins who had not used cannabis by age 17 years, those who had used cannabis by this age had elevated lifetime rates of other drug use, illicit drug abuse/dependence, and alcohol dependence.
2. The unadjusted conditional ORs indicated that in individuals who initiated cannabis use before age 17 years, the odds of other drug use, alcohol dependence, and other drug abuse/dependence were 2.1 to 5.2 times higher than in their co-twins who did not report early cannabis use. In all but 1 comparison (sedative abuse/dependence), these associations were statistically significant.

3. Controlling for known risk factors for later drug use and drug abuse/dependence had only negligible effects. Specifically, after such adjustment, relative to their discordant co-twins, those who had used cannabis before age 17 years had significantly elevated rates of 9 of the 10 outcomes. The nonsignificant association between early cannabis use and sedative abuse/dependence is likely to be a reflection of reduced statistical power due to the low base rate of this outcome.

The final column of Table 2 shows the significant or marginally significant ($P<.10$) predictors of each outcome. While covariates differed between equations, early regular use of tobacco and alcohol emerged as the 2 factors most consistently associated with later illicit drug use and abuse/dependence. While early regular alcohol use did not emerge as a significant independent predictor of alcohol dependence, this finding should be treated with considerable caution, as our study did not provide an optimal strategy for assessing the effects of early alcohol use.

Analyses Restricted to Those Reporting Lifetime Cannabis Use

Our analysis found that 24.8% of twins in pairs discordant for early cannabis use in fact reported *no* lifetime cannabis use. To examine the extent to which the asso-

Table 3. Drug Use Outcomes in Twin Pairs Discordant for Cannabis Use Before Age 17 Years With Sample Restricted to Those Reporting Lifetime Cannabis Use (N = 234 Pairs)

	Lifetime Prevalence		Unadjusted Conditional OR (95% CI)	Conditional OR Adjusted for Covariates	
	Early Cannabis Users, No. (%)	Co-twins, No. (%)		OR (95% CI)	Significant Covariates*
Use					
Sedatives	46 (19.7)	20 (8.5)	3.00 (1.60-5.62)	3.33 (1.53-7.23)	1, 4
Hallucinogens	94 (40.2)	56 (23.9)	3.92 (2.13-7.21)	3.92 (2.13-7.21)	...
Cocaine/stimulants	123 (52.6)	81 (34.6)	3.00 (1.83-4.92)	3.05 (1.75-5.33)	1, 2
Opioids	33 (14.1)	17 (7.3)	2.33 (1.19-4.59)	2.40 (1.05-5.49)	4
Illicit drug abuse/dependence					
Cannabis	121 (51.7)	99 (42.3)	1.58 (1.05-2.37)	1.57 (0.98-2.52)	1, 2, 5
Sedatives	6 (2.6)	1 (0.4)	6.00 (0.72-49.83)	6.00 (0.72-49.83)	...
Cocaine/stimulants	36 (15.4)	13 (5.6)	4.29 (1.88-9.76)	3.79 (1.60-9.01)	3
Opioids	10 (4.3)	2 (0.9)	5.00 (1.10-22.82)	5.00 (1.10-22.82)	...
Any illicit drug abuse/dependence	127 (54.3)	100 (42.7)	1.75 (1.16-2.64)	1.76 (1.08-2.84)	1, 2, 5
Alcohol dependence	109 (46.6)	79 (33.8)	2.03 (1.30-3.17)	1.85 (1.21-2.83)	3, 4

Abbreviations: CI, confidence interval; OR, odds ratio.

*For significant covariates, 1 indicates early (before age 17 years) regular use of tobacco; 2, early (before age 17 years) regular use of alcohol; 3, conduct disorder; 4, major depression; and 5, social anxiety. Ellipses indicate that there were no significant covariates for the outcome.

ciations in Table 2 may have been related to risks associated with *any* cannabis use rather than *early* cannabis use, these analyses were replicated with the sample restricted to those who reported lifetime cannabis use (54 monozygotic female pairs, 53 monozygotic male pairs, 56 dizygotic female pairs, 71 dizygotic male pairs). The results of these analyses, shown in TABLE 3, were broadly consistent with the previous results. In particular, before adjustment for covariates, early use remained a significant predictor of all but 1 of the outcomes (sedative abuse/dependence) among twin pairs concordant for lifetime cannabis use but where 1 twin reported initiation of cannabis use before age 17 years and the other did not. After statistical control for measured risk factors, early use was not a significant predictor of sedative abuse/dependence, and there was only a marginally significant association ($P=.06$) between early initiation of cannabis use and subsequent abuse/dependence on cannabis.

Subsidiary Analyses

Separate analyses of monozygotic- and dizygotic-discordant pairs were conducted in which early cannabis use was defined as use before age 15 years, before age 16 years, and before age 18 years. The results of these analyses con-

firmed the previous conclusions. For all definitions of early cannabis use, individuals who initiated cannabis use at an early age had elevated odds of later drug use and abuse/dependence relative to their discordant co-twin.

COMMENT

The results of our co-twin control analyses indicated that early initiation of cannabis use was associated with significantly increased risks for other drug use and abuse/dependence and were consistent with early cannabis use having a causal role as a risk factor for other drug use and for any drug abuse or dependence. Individuals who used cannabis before age 17 years had a 2.3- to 3.9-fold increase in odds of other drug use and a 1.6- to 6.0-fold increase in odds of alcohol dependence and other drug abuse/dependence, relative to their co-twin who had not used cannabis by age 17 years, regardless of whether or not the pair were monozygotic. Alternatively, there may be unmeasured environmental influences not shared by members of a twin pair that increase risks both of early cannabis use and of other drug use or abuse/dependence. We consider this less plausible, since twin pairs, having been reared in the same household, would be expected to be highly concordant for environmental experi-

ences. Unmeasured family background risk factors or heritable risk factors cannot explain the observed association, since twin pairs will share the same family background, and monozygotic pairs the same genetic risk factors.

Potential limitations of this study include the reliance on self-report and retrospective data, and the lack of data about ages at progression to more frequent use or onset of problems. Age of first use was obtained earlier in our interview than the assessment of drug use problems to minimize recall biases; and the associations with early cannabis use that we observed in this twin pair sample have previously been reported in prospective studies.¹⁶⁻¹⁹ An association due to underreporting of drug use by 1 twin seems implausible, since cannabis use, even by self-report, was highly prevalent and some use at least would be considered normative for this birth cohort in Australia, and since significant associations remained when analyses were limited to pairs concordant for lifetime cannabis use. It is also unlikely that we are observing only delayed onset of other drug use or drug abuse/dependence, rather than lower lifetime rates in the co-twins, since the median age of the sample (30 years) is considerably higher than typical ages of onset of drug use and drug abuse/

dependence.³³ For example, more than 95% of cannabis users in our total sample reported onset of marijuana use by age 24 years, the youngest age represented in the sample. Our estimates of the lifetime use of cannabis and other drugs are high but are consistent with those reported by other large-scale epidemiological surveys of drug use in Australia.³⁴ Further, a recent study of cannabis use in a US national twin sample concluded that twin studies of substance use are unlikely to be biased and that findings from such studies can be generalized to other (non-twin) family relationships.³⁵ The relative crudeness of our measure of exposure (any use before age 17 years as opposed to frequent, heavy, or problem use) makes the findings of an association even more remarkable.

If the association with early cannabis use is indeed causal, the mechanisms by which this association arises remain unclear. Pharmacological mechanisms might be hypothesized in which it is assumed that exposure to cannabis induces subtle biochemical changes that encourage drug-taking behavior.³⁶ This hypothesis is supported to some extent by recent findings that Δ^9 -tetrahydrocannabinol and heroin have similar effects on dopamine transmission through a common μ_1 opioid receptor mechanism³⁷ and that chronic treatment with Δ^9 -tetrahydrocannabinol induces cross-tolerance to amphetamine³⁸ and opioids^{38,39} in rats. However, an argument against such biological hypotheses is that the levels of cannabis use at the beginning of drug-using careers are substantially lower than the equivalents used in laboratory-based research and perhaps too low to induce long-term biochemical changes.

Other mechanisms that might mediate a causal association between early cannabis use and subsequent drug use and drug abuse/dependence include the following:

1. Initial experiences with cannabis, which are frequently rated as pleasurable,⁴⁰ may encourage continued use of cannabis and also broader experimentation.

2. Seemingly safe early experiences with cannabis may reduce the perceived risk of, and therefore barriers to, the use of other drugs. For example, as the vast majority of those who use cannabis do not experience any legal consequences of their use, such use may act to diminish the strength of legal sanctions against the use of all drugs.

3. Alternatively, experience with and subsequent access to cannabis use may provide individuals with access to other drugs as they come into contact with drug dealers.⁴¹ This argument provided a strong impetus for the Netherlands to effectively decriminalize cannabis use in an attempt to separate cannabis from the hard drug market.¹² This strategy may have been partially successful as rates of cocaine use among those who have used cannabis are lower in the Netherlands than in the United States.⁴²

While the findings of this study indicate that early cannabis use is associated with increased risks of progression to other illicit drug use and drug abuse/dependence, it is not possible to draw strong causal conclusions solely on the basis of the associations shown in this study. Further research in other cultures and using a range of innovative research designs (including evaluation of prevention efforts aimed at delaying the onset of cannabis use) is needed to explore whether there is a causal link between early cannabis use and progression to other drug use and, if so, to elucidate the mechanisms that may underlie any such causal association.

Regardless of the mechanisms underlying these associations, it is apparent that young people who initiate cannabis use at an early age are at heightened risk for progressing to other drug use and drug abuse/dependence. In addition to cannabis dependence, the health risks associated with chronic cannabis use may include chronic bronchitis, impaired lung function, and increased risks of cancers of the aerodigestive tract.⁴ Given historical increases in the use of cannabis and other drugs,^{1,2} it is probable that more individuals will experience these adverse consequences and

there will be an increasing need to develop strategies both to prevent and to ameliorate the adverse consequences of chronic drug use. Given that early initiation of use may be associated with increased risks both for progressing to the use of other drugs and for developing drug abuse/dependence, there is a need for greater physician awareness of those risks associated with early use. There is also a need to develop focused interventions to prevent escalation to use of other drugs among young people identified as being at risk due to their early initiation of cannabis use.

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Acquisition of data: Heath, Bucholz, Slutske, Madden, Statham, Martin.

Analysis and interpretation of data: Lynskey, Heath, Nelson, Slutske.

Drafting of the manuscript: Lynskey, Heath.

Critical revision of the manuscript for important intellectual content: Bucholz, Slutske, Madden, Nelson, Statham, Martin.

Statistical expertise: Lynskey, Heath, Martin.

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REFERENCES

- Bachman JG, Johnston LD, O'Malley PM. Explaining recent increases in students' marijuana use: impacts of perceived risks and disapproval, 1976 through 1996. *Am J Public Health.* 1998;88:887-892.
- Reid A, Lynskey MT, Copeland J. Cannabis use among Australian youth. *Aust N Z J Public Health.* 2000;24:596-602.
- Substance Abuse and Mental Health Services Administration. The DASIS Report: Marijuana treatment admissions increase: 1993-1999. Available at: <http://www.samhsa.gov/oas/2k2/MJtx.pdf>. Accessed May 17, 2002.
- Hall W, Solowij N. Adverse effects of cannabis. *Lancet.* 1998;352:1611-1616.
- Solwijn N, Stephens RS, Roffman RA, et al. Cognitive functioning of long-term heavy cannabis users seeking treatment. *JAMA.* 2002;287:1123-1131.
- McLellan AT, Lewis DC, O'Brien CP, Kleber HD. Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. *JAMA.* 2000;284:1689-1695.
- Substance Abuse and Mental Health Services Administration. The DASIS Report: Treatment referral sources for adolescent marijuana users. Available at: <http://www.samhsa.gov/oas/2k2/YouthMJtx/YouthMJtx.pdf>. Accessed May 17, 2002.
- Kandel DB. Stages in adolescent involvement in drug use. *Science.* 1975;190:912-914.

9. Kandel DB, Faust R. Sequences and stages in patterns of adolescent drug use. *Arch Gen Psychiatry*. 1975;32:923-932.
10. Kandel DB, Yamaguchi K, Chen K. Stages of progression in drug involvement from adolescence to adulthood: further evidence for the gateway theory. *J Stud Alcohol*. 1992;53:447-457.
11. MacCoun R. In what sense (if any) is marijuana a gateway drug? FAS Drug Policy Analysis Bulletin, 1998; Issue 4. Available at: <http://www.fas.org/drugs/issue4.htm#gateway>. Accessed May 17, 2002.
12. Ellickson PL, Hayes RD, Bell RM. Stepping through the drug use sequence: longitudinal scalogram analysis of initiation and regular use. *J Abnorm Psychol*. 1992;101:441-451.
13. Graham JW, Collins LM, Wugalter SE, Chung NK, Hansen WB. Modeling transitions in latent stage-sequential processes: a substance use prevention example. *J Consult Clin Psychol*. 1991;59:48-57.
14. Baumrind D. Specious causal attribution in the social sciences: the reformulated steeping stone hypothesis as exemplar. *J Pers Soc Psychol*. 1983;45:1289-1298.
15. Yamaguchi K, Kandel DB. Patterns of drug use from adolescence to young adulthood, III: predictors of progression. *Am J Public Health*. 1984;74:673-681.
16. Fergusson DM, Horwood LJ. Early onset cannabis use and psychosocial adjustment in young adults. *Addiction*. 1997;92:279-296.
17. Fergusson DM, Horwood LJ. Does cannabis use encourage other forms of illicit drug use? *Addiction*. 2000;95:505-520.
18. 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. *J Subst Abuse*. 1998;10:163-173.
19. Kosterman R, Hawkins JD, Guo J, Catalaon RF, Abbott RD. The dynamics of alcohol and marijuana initiation: patterns and predictors of first use in adolescence. *Am J Public Health*. 2000;90:360-366.
20. Lynskey MT, Heath AC, Nelson EC, et al. Genetic and environmental contributions to cannabis dependence in a national young adult twin sample. *Psychol Med*. 2002;32:195-207.
21. 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. *Arch Gen Psychiatry*. 2000;57:261-269.
22. Tsuang MT, Lyons MJ, Meyer JM, et al. Co-occurrence of abuse of different drugs in men: the role of drug-specific and shared vulnerabilities. *Arch Gen Psychiatry*. 1998;55:967-972.
23. Nelson EC, Heath AC, Madden PAF, et al. The consequences and correlates of childhood sexual abuse—a retrospective examination using the twin study design. *Arch Gen Psychiatry*. 2002;59:139-145.
24. Heath AC, Howells W, Kirk KM, et al. Predictors of non-response to a questionnaire survey of a volunteer twin panel: findings from the Australian 1989 twin cohort. *Twin Res*. 2001;4:73-80.
25. Cederlof R, Friberg L, Jonsson E, Kaij L. Studies on similarity diagnosis in twins with the aid of a mailed questionnaire. *Acta Genetica et Statistica Medica*. 1961;11:338-362.
26. Kasriel J, Eaves LJ. The zygosity of twins: further evidence on the agreement between diagnosis by blood groups and written questionnaires. *J Biosoc Sci*. 1976;8:263-266.
27. Nichols RC, Bilbro WC Jr. The diagnosis of twin zygosity. *Acta Genet Stat Med*. 1966;16:265-275.
28. Sarna S, Kaprio J, Sistonen P, Koskenvuo M. Diagnosis of twin zygosity by mailed questionnaire. *Hum Hered*. 1978;28:241-254.
29. Bucholz KK, Cloninger CR, Dinwiddie SH, et al. A new, semi-structured psychiatric interview for use in genetic linkage studies: a report of the reliability of the SSAGA. *J Stud Alcohol*. 1994;55:149-158.
30. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association; 1994.
31. SAS Institute Inc. *SAS/STAT Software: Changes and Enhancements for Release 6.12*. Cary, NC: SAS Institute Inc; 1996.
32. StataCorp. *Stata Statistical Software: Release 6.0*. College Station, Tex: Stata Corp; 1999.
33. Chen K, Kandel DB. The natural history of drug use from adolescence to the mid thirties in a general population sample. *Am J Public Health*. 1995;85:41-47.
34. Australian Institute of Health and Welfare. *1998 National Drug Strategy Household Survey: First Results*. Canberra: Australian Institute of Health and Welfare; 1999.
35. Kendler KS, Neale MC, Thornton LM, Aggen SH, Gilman SE, Kessler RC. Cannabis use in the last year in a US national sample of twin and sibling pairs. *Psychol Med*. 2002;32:551-554.
36. Nahas G. *Keep Off the Grass*. Middlebury, Vt: Paul Eriksson; 1990.
37. Tanda G, Pontieri F, Di Chiara G. Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common mu 1 opioid receptor mechanism. *Science*. 1997;276:2048-2050.
38. Lamarque S, Taghouzti K, Simon H. Chronic treatment with Δ^9 -tetrahydrocannabinol enhances the locomotor response to amphetamine and heroin: implications for vulnerability to drug addiction. *Neuropharmacology*. 2001;41:118-129.
39. Cadoni C, Pisanu A, Solinas M, Acqua E, Di Chiara G. Behavioural sensitization after repeated exposure to Δ^9 - tetrahydrocannabinol and cross-sensitization with morphine. *Psychopharmacology*. 2001;158:259-266.
40. Fergusson DM, Lynskey MT, Horwood LJ. Patterns of cannabis use among 13-14 year old New Zealanders. *N Z Med J*. 1993;106:247-250.
41. Cohen H. Multiple drug use considered in the light of the stepping-stone hypothesis. *Int J Addict*. 1972;7:27-55.
42. MacCoun R, Reuter P. Evaluating alternative cannabis regimes. *Br J Psychiatry*. 2001;178:123-128.