

Cannabis and Anxiety and Depression in Young Adults: A Large Prospective Study

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ABSTRACT

Objective: To examine whether age of first use or frequency of use of cannabis is associated with anxiety and depression (AD) in young adults, independent of known potential confounders, including the use of other illicit drugs. **Method:** A cohort of 3,239 Australian young adults was followed from birth to the age of 21 when data on AD were obtained from sample members along with information on their use of cannabis at 21 years. Potential confounding factors were prospectively measured when the child was born and at 14 years. **Results:** After controlling for confounding factors, those who started using cannabis before age 15 years and used it frequently at 21 years were more likely to report symptoms of AD in early adulthood (odds ratio 3.4; 95% CI 1.9–6.1). This association was of similar magnitude for those who had only used cannabis and those who reported having used cannabis and other illicit drugs. **Conclusion:** The relationship between early-onset and frequent use of cannabis and symptoms of AD is independent of individual and family backgrounds. Frequent cannabis use is associated with increased AD in young adults independently of whether the person also uses other illicit drugs. *J. Am. Acad. Child Adolesc. Psychiatry*, 2007;46(3):408–417. **Key Words:** anxiety and depression, cannabis, young adult.

In adolescents and young adults, use of cannabis has been associated with symptoms of mental illness in both cross-sectional surveys (Degenhardt et al., 2001; Lynskey et al., 2004; Rey et al., 2002) and longitudinal studies (Bovasso, 2001; Brook et al., 2002; Fergusson

et al., 2002; McGee et al., 2000; Patton et al., 2002). Nonetheless, questions remain about the direction of the association between use of cannabis and anxiety and depression (AD). Three models have been proposed to explain this relationship (Degenhardt et al., 2003). The first is a common factor model that proposes the association between cannabis and AD as a reflection of common biological and/or environmental etiologies (Brook et al., 1998). These factors include genetic (Kendler and Prescott, 1998; Kendler et al., 1992) and environmental factors (Gilman et al., 2003; Kessler et al., 1994; McGee et al., 2000) such as socioeconomic status, parental marital status, cigarette smoking, and alcohol consumption. Several researchers have examined this hypothesis (Fergusson et al., 2002; Kandel et al., 1986; McGee et al., 2000) and suggested that the association is independent of third factors.

The second model is AD leads to cannabis use. The association could arise because people with mental health problems are more likely to use cannabis, perhaps in response to their symptoms (Khantzian, 1985). Despite positive findings from cross-sectional surveys (Henry et al., 1993), prospective studies have

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failed to demonstrate a significant relationship between AD and later use or abuse of cannabis (Brook et al., 1998; Henry et al., 1993; Hofstra et al., 2002).

The third model is cannabis use leads to mental health problems. Although inconsistent, the evidence concerning this model appears stronger than for the other alternatives. Most of the prospective studies have found an increase in symptoms of AD after cannabis use (Bovasso, 2001; Brook et al., 1998; Fergusson et al., 2002; McGee et al., 2000; Patton et al., 2002); however, some others have failed to find this association (Fergusson et al., 1996; Kandel et al., 1986). The reasons for these discrepancies may be lack of long-term follow-up (Fergusson et al., 1996) and failure to distinguish between use of cannabis alone and its co-use with other illicit drugs (Kandel et al., 1986).

Overall, there remains a paucity of evidence of whether age of initiation to use of cannabis and its frequency of use predict risk of AD in early adulthood. It is hypothesized that individuals who begin using cannabis in early adolescence and use it frequently are at increased risk of AD in early adulthood. Furthermore, it has been found that individuals who initiated the use of cannabis in early adolescence are more likely to subsequently abuse cannabis and to use other illicit drugs (Fergusson et al., 1996, 2002). Therefore, there is a need to test the association separately for cannabis-only users and for those who have used cannabis along with other illicit drugs. We examined different scenarios linking cannabis and AD using a 21-year birth cohort longitudinal data set.

METHOD

Participants

The data we used were taken from the 21-year Mater University Study of Pregnancy (MUSP; Najman et al., 2005). After piloting, it was clear that the cost and effort required to recruit privately insured patients were prohibitive (many obstetricians at varied sites). Consequently, privately insured pregnant women (39%) and emergencies transferred to this specialist obstetric service were excluded and 8,556 consecutive patients (at an average of 18 weeks of gestation) were invited to participate in the study. Of these, 8,458 (99%) agreed to complete the recruitment questionnaire and 7,223 mothers and their live singleton babies constituted the overall birth cohort (Fig. 1). Mothers were reinterviewed 3 to 5 days after the birth of their child, and again when the child was 6 months and 5, 14, and 21 years of age. Children were also interviewed at the 14- and 21-year follow-ups. For the purpose of this study, 4,861 adolescents who provided information at 14 years were included, of whom 3,239 (66.6%) completed the 21-year questionnaire about

use of cannabis and AD. Data on use of other illicit drugs were available for 3,157 of these young adults. Written informed consent from the mother was obtained at all data collection phases and from the young adult at the 21-year follow-up of the study. Ethics committees at the Mater Hospital and the University of Queensland approved each phase of the study.

Measures

Adolescent/Young Adult AD. AD are frequently associated with each other in both community and psychiatric settings (Armstrong and Costello, 2002). In the present study, symptoms of AD during the past 6 months were measured at 21-year follow-up using the Young Adult Self-Report (YASR) version of the Child Behavior Checklist (Achenbach, 1997). The YASR is a questionnaire for subjects ages 18 to 30 years. It contains 110 items that can potentially identify eight clinical syndromes, including AD. The YASR provides the capacity to compare the behaviors of the child, adolescent, and young adult using a consistent standardized measure (Wiznitzer et al., 1992). The items in each subscale of the YASR have good reliability and are associated with *DSM-III-R* diagnoses obtained from structured interviews (Achenbach, 1997).

Symptoms of AD as well as externalizing behavior (aggression and delinquency) in the adolescents at 14 years were assessed using the Youth Self-Report (YSR; Achenbach, 1991), which is a self-report questionnaire for subjects ages 11 to 18 years and asks about feelings in the past 6 months. The YASR and YSR share items and, like the YASR, the YSR has good reliability and validity (Wiznitzer et al., 1992). Furthermore, scores on the AD subscales of the YSR and YASR correlate well over an interval of 10 years (Visser et al., 2000). In the present study, cases of AD at both 14 and 21 years were selected using a 10% cutoff of scores on the relevant subscale. This cutoff represents the optimum numbers for allocating individual children to the affected group based on assessments of the sensitivity and specificity of the scale (Achenbach and Edelbrock, 1983).

Cannabis Use. Consumption of cannabis was retrospectively assessed at the 21-year follow-up via self-reported answers to two questions. The first concerned frequency of use of cannabis in the past month (never used, used every day, every few days, once in the past month, and not in the past month). All of the participants were then asked the age at which they first used cannabis (answers other than "never used" ranged between 7 and 21 years). Apart from 1,653 (51%) young adults who answered "never used" to both questions, the remainder were considered cannabis-ever users. Consistent with previous studies (Fergusson et al., 1996), we regarded first use of cannabis at 14 years of age and younger as early use. Based on the frequency of use reported at the 21-year follow-up, ever-users of cannabis were divided into two categories, occasional use and frequent use, referring to use of cannabis once in past month or not in the past month and every day or every few days, respectively.

Previous studies have suggested that early initiation to use of cannabis increases the risk of later cannabis disorders and use of other illicit drugs. In the present study, we assessed both age at onset and frequency of use of cannabis at the 21-year follow-up. Preliminary analyses indicated that age at onset of cannabis use was highly correlated with frequency of use of cannabis at 21 years (Spearman's correlation = 0.90, $p < .0001$). Therefore, using these two variables (age of onset and frequency of use), we divided the young adults into five categories as follows: nonusers of cannabis; those who started to use cannabis in late adolescence and used it

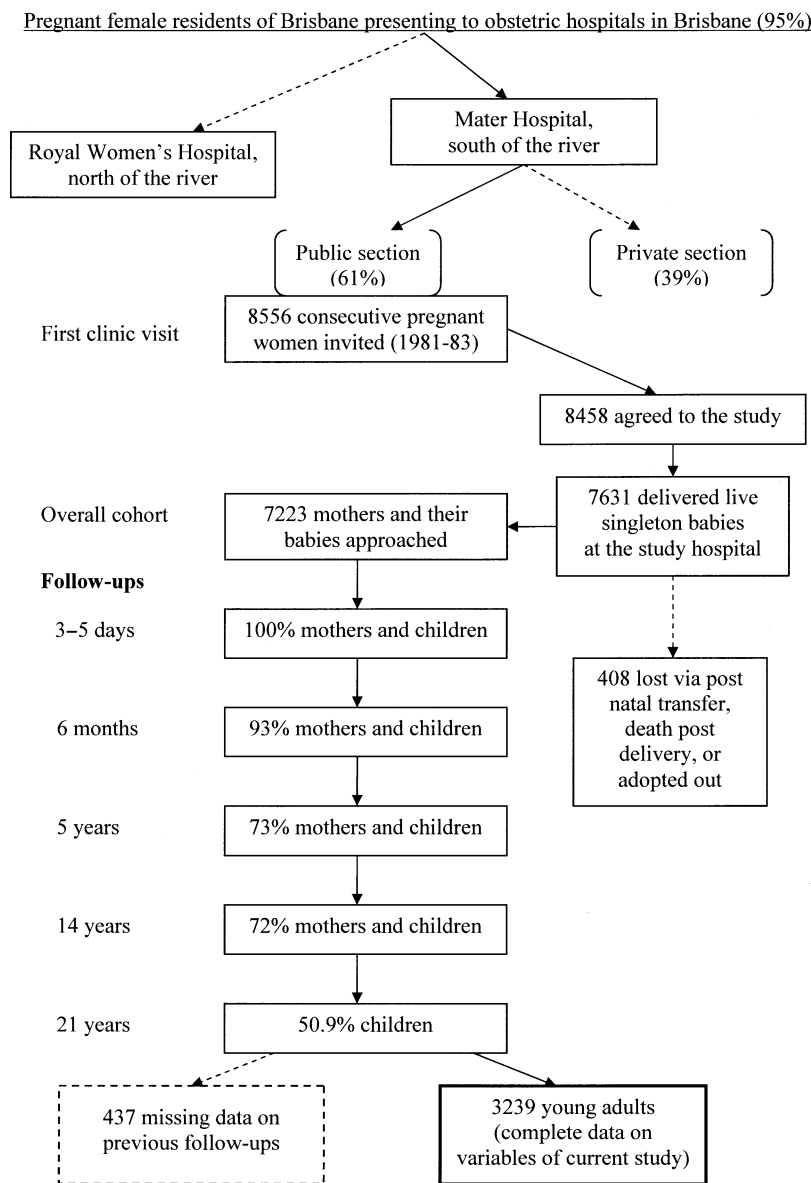


Fig. 1 Sampling frame and follow-ups of the Mater University Study of Pregnancy.

occasionally in early adulthood; those who started to use cannabis in early adolescence and used it occasionally in early adulthood; those who started to use cannabis in late adolescence and used it frequently in early adulthood; and those who started to use cannabis in early adolescence and used it frequently in early adulthood.

Confounding Factors. We adjusted the association between cannabis and AD for the child's gender, mother's age and education, maternal marital status and quality, family income, maternal mental health, maternal substance use, adolescent's mental health, and adolescent smoking status and alcohol consumption at the 14-year follow-up. Mother's age (two categories: 13–19 years and 20 years and older) and level of education at time of birth (having post-high school education, completed high school, and those who did not complete high school) and gross family income at the 14-year follow-up were used as indicators of socioeconomic

status. We selected the 25th centile at the 14-year follow-up as the cutoff below which gross family income was defined as low.

Maternal marital status was self-reported by mothers at the 14-year follow-up as being unpartnered or living with the child's biological or stepfather. The quality of maternal marital relationships at 14 years was assessed using a short form of the Dyadic Adjustment Scale (Spanier, 1976). Mothers were divided into three categories: unpartnered group, partnered mothers with good adjustment, and partnered mothers with poor adjustment. Combining these two variables, we distinguished five types of marital circumstances: intact families with good adjustment, intact families with poor adjustment, nonintact families (mother and stepfather) with good adjustment, nonintact families with poor adjustment, and unpartnered mothers (who were divorced, separated, widowed, or never married).

Maternal mental health at the 14-year follow-up was assessed using the short form of the Delusions-Symptoms-States Inventory (Bedford and Foulds, 1978). This inventory has been validated extensively and has been used in numerous studies (Bagshaw, 1977). For the purpose of this study, mothers were classified as anxious or depressed if they reported three or more of seven symptoms related to anxiety or depression, respectively. Maternal cigarette smoking and alcohol consumption (referred to as maternal substance use) were assessed at the 14-year follow-up, and mothers were classified as smokers/nonsmokers and abstainers/drinkings.

The extent of smoking and drinking by the youths at 14 years was assessed via questions concerning the average number of cigarettes smoked and glasses of alcohol consumed per day during the week preceding the survey. Subjects were then divided into two categories: nonsmokers/smokers and abstainers/drinkings. Use of illicit drugs other than cannabis during the year preceding the survey was assessed at 21 years by self-report. Subsequently, participants were divided into two categories: never used and used.

Statistical Analyses

We used contingency tables and logistic regression to examine the association between a range of potential explanatory factors and suspected confounders, use of cannabis, and symptoms of anxiety or depression in young adults. To test whether AD in early adolescence predicts later use of cannabis, we first excluded 385 adolescents who recalled (at 21 years) having used cannabis before 15 years of age. We then used multinomial logistic regression (Leyland and Goldstein, 2001) to examine the univariate and multivariate associations between symptoms of AD at 14 years and occasional or frequent use of cannabis by young adults. To test the opposite direction of association, we first examined the association of age at initiation and frequency of use of cannabis with young adults' symptoms of AD. Subsequently, we combined two self-reported variables (age at onset and frequency of use) and investigated whether these variables predicted young adults' symptoms of AD.

Next, we fitted successive multivariate models to examine the effect of confounders. We divided these variables into three domains: sociodemographic factors including child's gender, mother's education, family income, and maternal marital status and quality; maternal mental health and substance use; and adolescent problem behavior and substance use. We first adjusted for sociodemographic factors (model 1). Subsequent models progressively included maternal mental health and substance use at 14 years (model 2), and the adolescent's mental health and smoking and alcohol consumption at 14 years (model 3). To distinguish the possible impact of other illicit drugs on the association between cannabis and AD, we divided cannabis users into two groups, cannabis only and cannabis and other illicit drugs, and repeated the multivariate adjustment for the new variable.

Furthermore, to examine the validity of the results, we tested the associations between age at onset and frequency of use of cannabis with clinical diagnoses of major depression and generalized anxiety/phobia disorders. We used the computerized version of the Composite International Diagnostic Interview (World Health Organization, 1992) to identify young adults with at least one criterion of affective disorders or total anxiety/panic/phobia disorders, according to *DSM-IV* diagnostic criteria. The results of the unadjusted and adjusted models are presented as odds ratios (ORs) together with 95% confidence intervals (CIs) as the level of statistical significance. All of the analyses were carried out using SPSS V.13 and STATA V.9.

Of the cohort of 4,861 mothers and children at the 14-year follow-up, 66.6% (3,239) completed the 21-year survey. Non-response was mainly predicted by mother's marital status and mental health, family income, and the adolescent's smoking and alcohol consumption at the 14-year follow-up. To assess whether nonresponse biased our results, we used inverse-probability weighting (Hogan et al., 2004). The probability weights were computed by using a logistic regression model with the outcome being complete or incomplete data and the independent variables being all other covariates used in our primary analyses. The regression coefficients from this model were then used to determine probability weights for the covariates in the main analyses. For example, if, based on the predictive model, the probability of nonresponse was 0.34 for an adolescent who smoked cigarettes at 14 years, his or her inverse weight was 2.94. The results from the analyses weighted by inverse probabilities did not differ from the unweighted analyses presented here, suggesting that our results were not substantially affected by selection attrition bias.

RESULTS

Overall, 3,239 young adults provided information about age at onset and frequency of use of cannabis and about AD. Some 49.0% had used cannabis, comprising 36.8% who reported use of cannabis once in the past month or no use in the past month (occasional users) and 12.2% who had used cannabis at least every few days in the past month (frequent users). Age at initiation to use of cannabis ranged between 7 and 21 years (mean 15.8, SD 1.9 years). Of 1,586 participants who had ever used cannabis, 24.3% reported starting to use cannabis before 15 years and 75.7% were late-onset users. Young adult scores for AD on the YASR ranged between 0 and 34 (mean 8.1, SD 6.5) and the extreme 10% cutoff included those who scored ≥ 18 .

Table 1 shows unadjusted associations between a selected group of explanatory variables and potential confounders measured at the time when child was 14 years old or earlier and symptoms of AD and use of cannabis in young adulthood. There were significant associations between AD symptoms in young adults, defined by the extreme decile of response to the YASR, and sex of the child, maternal marital status, maternal anxiety, adolescent mental health, and substance use when the child was 14 years old. Females were more likely to have symptoms of AD at 21 years. The individuals who, at 14 years, were categorized as anxious/depressed and those who had aggression/delinquency behavior had a higher prevalence of AD in early adulthood, as did those children who smoked cigarettes at 14 years. Adolescent AD at 14 years was the strongest predictor for AD in young adults.

TABLE 1
Young Adult AD and Cannabis Ever Use by Background Factors (*N* = 3,239)

Covariates ^a	No.	Unadjusted OR (95% CI)	
		AD	Cannabis
Child gender			
Male	1,547	1.0	1.0
Female	1,692	2.1 (1.6–2.7)	0.8 (0.7–0.9)
Mother's age ^b			
≥20 y	2,819	1.0	1.0
<20 y	420	1.0 (0.7–1.4)	1.1 (0.9–1.4)
Mother's education ^b			
Post-high school	650	1.0	1.0
Complete high school	2,112	0.8 (0.6–1.1)	1.2 (1.0–1.4)
Incomplete high school	477	1.2 (0.8–1.7)	1.2 (0.9–1.5)
Family income			
Middle and high	2,639	1.0	1.0
Low income	600	1.2 (0.9–1.6)	1.2 (1.0–1.4)
Maternal marital status			
Intact, good quality	1,797	1.0	1.0
Intact, poor quality	503	1.3 (0.9–1.8)	1.6 (1.3–1.9)
Nonintact, good quality	413	1.2 (0.9–1.8)	2.5 (2.0–3.1)
Nonintact, poor quality	145	1.2 (0.7–2.1)	2.3 (1.6–3.2)
Unpartnered	381	1.5 (1.0–2.1)	1.7 (1.4–2.2)
Maternal mental health			
Depressed	353	1.2 (0.9–1.7)	1.4 (1.1–1.7)
Anxious	915	1.2 (1.0–1.6)	1.3 (1.1–1.5)
Maternal smoking			
Nonsmoker	2,336	1.0	1.0
Smoker	906	1.2 (0.9–1.5)	1.7 (1.5–2.0)
Maternal alcohol consumption			
Nondrinker	573	1.0	1.0
Drinker	2,666	0.8 (0.6–1.1)	1.6 (1.4–2.0)
Adolescent mental health ^c			
Anxious/depressed	299	4.9 (3.6–6.5)	1.4 (1.1–1.8)
Aggressive/delinquent	287	1.9 (1.3–2.6)	4.2 (3.1–5.5)
Adolescent's smoking			
Nonsmoker	2,898	1.0	1.0
Smoker	341	1.6 (1.1–2.2)	5.3 (4.0–7.0)
Adolescent alcohol use			
Nondrinker	2,113	1.0	1.0
Drinker	1,126	1.2 (0.9–1.5)	2.6 (2.2–3.0)

Note: OR = odds ratio; AD = anxiety and depression.

^a Assessed at the 14-year follow-up unless otherwise indicated.

^b Assessed at the child's birth.

^c Dichotomous variables; data are row% for positive stratum of 2 × 2 tables.

Table 1 also suggests that females were moderately less likely to use cannabis by early adulthood. All types of household other than intact family, good adjustment, at 14 years predicted an increase in risk of cannabis use at 21 years with the strongest association observed in children who were raised in nonintact families. Presence of maternal anxiety or depression,

maternal smoking, or maternal alcohol consumption when the child was age 14 was associated with greater risk of later cannabis use in the child. Use of cannabis by early adulthood was more common among those who had symptoms of AD or aggression/delinquency, smoked cigarettes, or used alcohol at 14 years. Adolescent aggression/delinquency and smoking were

TABLE 2
AD Predicting Later Use of Cannabis (*N* = 2,854)

		Use of Cannabis by Young Adults, ^a OR (95% CI) ^b			
AD at 14 y	No.	Occasional Use		Frequent Use	
		Unadjusted	Adjusted ^c	Unadjusted	Adjusted ^c
No	2,610	1.0	1.0	1.0	1.0
Yes	244	1.3 (1.0–1.7)	1.0 (0.8–1.4)	1.2 (0.8–1.9)	0.9 (0.6–1.6)

Note: AD = anxiety and depression.

^a After 14 y.

^b Never use considered reference category.

^c Adjusted for gender, mother's education, family income, marital status and quality, maternal mental health and substance use, and adolescent aggression/delinquency, and adolescent cigarette smoking and alcohol consumption at age 14 y.

the two strongest predictors of cannabis use in young adults.

To examine the association between AD in early adolescence with later cannabis use, we excluded 385 participants who recalled having used cannabis before the age of 15 years. Table 2 shows that there was no significant association (in either unadjusted or adjusted analyses) between symptoms of AD at 14 years and either occasional or frequent use of cannabis by young adults.

Table 3 shows the unadjusted and adjusted associations between age at onset and frequency of use of cannabis and AD symptoms at 21 years. In the unadjusted analysis, children who reported frequent use of cannabis were considerably more likely to report symptoms of AD

at 21 years relative to those who never used cannabis or tried it occasionally. Among frequent users (those using cannabis at least every few days), the risk was somewhat greater for those who started using it before 15 years of age (crude OR 2.5; 95% CI 1.6–4.0) compared with later onset (OR 1.8; 95% CI 1.2–2.7). Adjustment for the child's sex, family income, and maternal marital status at 14 years (model 1) enhanced the associations for frequent users of cannabis, regardless of age at onset of use. That was because AD was more common in females, whereas frequent use of cannabis was more common among males. Further adjustment for maternal mental health at 14 years (model 2) and adolescent cigarette smoking and alcohol consumption (model 3) did not significantly change the relationships.

We further examined the association between use of cannabis and symptoms of AD while using other illicit drugs taken into account among 3,157 young adults who provided information about previous use of illicit drugs other than cannabis. Because of the small number of participants who frequently used cannabis but not other illicit drugs, we were not able to divide cannabis-only users into early-onset and late-onset subgroups. Multivariate findings in Table 4 show that frequent use of cannabis, either without or with use of other illicit drugs, predicts a more than twofold increase in AD in young adults.

DISCUSSION

Using data from a birth cohort study, we examined three models of association between use of cannabis and

TABLE 3
Age at Onset and Frequency of Use of Cannabis Predicting AD in Young Adults (*N* = 3,239)

		AD in Young Adults (21 y), Odds Ratio (95% CI)			
Self-Reported Use of Cannabis	No.	Unadjusted	Adjusted		
			Model 1 ^a	Model 2 ^b	Model 3 ^c
Never used	1,653	1.0	1.0	1.0	1.0
Occasional use					
Late onset	950	1.2 (0.9–1.6)	1.2 (0.9–1.6)	1.2 (0.9–1.6)	1.2 (0.9–1.6)
Early onset	241	1.4 (0.9–2.2)	1.3 (0.8–2.1)	1.4 (0.9–2.2)	1.3 (0.8–2.1)
Frequent use					
Late onset	251	1.8 (1.2–2.7)	2.3 (1.5–3.6)	2.3 (1.5–3.6)	2.3 (1.5–3.6)
Early onset	144	2.5 (1.6–4.0)	3.1 (1.9–5.0)	3.2 (2.0–5.2)	3.0 (1.8–5.2)

Note: AD = anxiety and depression.

^a Controlled for child gender, mother's education, family income, maternal marital status and quality, and family income at 14 y.

^b Controlled for model 1 plus maternal mental health, smoking, and alcohol consumption at 14 y.

^c Controlled for model 2 plus adolescent anxiety and depression and aggression/delinquency, and adolescent smoking and alcohol consumption at 14 y.

TABLE 4
Risk of AD at 21 y by Use of Cannabis and Other Illicit Drugs (*N* = 3,157)

Self-Reported Use of Illicit Drugs	No.	AD in Young Adults (21 y) Odds Ratio (95% CI)			
		Unadjusted	Adjusted		
			Model 1 ^a	Model 2 ^b	Model 3 ^c
Never used any illicit drugs	1,573	1.0	1.0	1.0	1.0
Only cannabis					
Occasional use	712	1.1 (0.8–1.5)	1.1 (0.8–1.5)	1.1 (0.8–1.5)	1.1 (0.8–1.5)
Frequent use	107	1.5 (0.8–2.9)	1.9 (1.0–3.7)	1.9 (1.0–3.7)	2.1 (1.1–4.0)
Cannabis plus other illicit drugs					
Occasional use	478	1.5 (1.0–2.1)	1.5 (1.1–2.1)	1.5 (1.1–2.1)	1.4 (1.0–2.0)
Frequent use	287	2.3 (0.6–3.3)	2.8 (1.9–4.2)	2.9 (1.9–4.2)	2.7 (1.8–4.1)

Note: AD = anxiety and depression.

^a Controlled for child gender, mother's education, family income, and maternal marital status and quality at 14 y.

^b Controlled for model 1 plus maternal mental health, smoking, and alcohol consumption at 14 y.

^c Controlled for model 2 plus adolescent anxiety and depression and aggression/delinquency and adolescent smoking and alcohol consumption at 14 y.

AD. We found that the association between cannabis and AD is not explained by measured individual and social factors at baseline. Furthermore, symptoms of AD in early adolescence do not appear to predict a child's use of cannabis. However, age at onset and frequency of use of cannabis (both reported at 21 years) are significantly associated with symptoms of AD in young adults; MUSP participants who reported having used cannabis frequently are significantly more likely to show symptoms of AD, and a greater effect was apparent for early onset of use. These associations were not sensitive to inclusion of various explanatory factors and a selected range of confounding variables in the statistical models.

In agreement with previous studies, we found that the association between cannabis use and AD is not a reflection of a range of possible common factors. However, we were not able to allow for the potential impact of genetic factors. Our finding that AD at baseline does not regularly precede initiation of cannabis is consistent with most previous studies (Brook et al., 1998; Henry et al., 1993; Hofstra et al., 2002). However, a lack of association between AD at 14 years and use of cannabis at 21 years does not eliminate the possibility of reverse causality in which AD leads to cannabis use. Our study has not collected information about mental health status and use of cannabis between the ages of 14 and 21 years. Other studies with shorter intervals between follow-ups could examine the robustness of the current finding.

The present data support previous studies showing that use of cannabis in adolescence predicts later mental health problems (Bovasso, 2001; Brook et al., 2002; Fergusson et al., 2002; McGee et al., 2000; Patton et al., 2002), although the magnitude of associations is not consistent in these studies. This can be explained by differences in measurement of exposure, assessment of outcome, or duration of follow-up. However, our study contradicts the results in some other reports (Fergusson et al., 1996; Kandel et al., 1986; McGee et al., 2000).

There are a number of possible explanations for these disagreements. First, although one of the earliest studies reported that use of illicit drugs predicted severe psychiatric problems, strong interrelationships between use of different types of illicit drugs did not allow separate examination of the effect of cannabis alone (Kandel et al., 1986). Second, differences in the duration of follow-up may have prevented other authors from identifying an association between use of cannabis and impairment of mental health (Fergusson et al., 1996; McGee et al., 2000). Our study suggests that both younger age at initiation of use of cannabis and greater frequency of use are associated with an increased risk of AD at 21 years.

There are several possible explanations for the association of cannabis and AD. One possibility is that long-term exposure to large doses of cannabis may affect a variety of neurotransmitters in a way that produces depressive symptoms (De Fonseca et al., 2005). In a study on rats Tsou and colleagues (1999)

found that endocannabinoids, via GABAergic interneurons, activate the CB1 receptor, which is present in the hippocampus and may potentiate behavioral and affective patterns. In humans placebo-controlled trials in patients with cancer show that cannabinoids produce dysphoria and depression (Tramer et al., 2001). These results cannot be generalized to the whole population as such short-term effects may not necessarily persist with longer term use.

A second possibility is that frequent use of cannabis may lead to adverse social and psychological consequences that are associated with the development of mental health impairment. These intermediate correlates include educational failure, school dropout, loss of job, and involvement in crime (Degenhardt et al., 2003; Kandel et al., 1986). On short-term follow-up of the consequences of cannabis use, Fergusson et al. (1996) did not find a significant association with impaired mental health. However, early onset of cannabis use did predict school dropout and was associated with increased risks of truancy or police contact, confirming the potential role of adverse psychosocial consequences in long-term outcomes of cannabis use. Social failure and being involved with antisocial groups may not only enhance the quantity of use but also could increase risk of mental health problems.

Use of cannabis, in particular, its early use, is associated with use of other illicit drugs (Kandel et al., 1986), and this latter behavior may increase the risk of mental health problems, either directly or through other psychosocial dynamics. However, our data show that the association of frequent use of cannabis with increased symptoms of AD in young adults remains significant when use of other illicit drugs is taken into account.

Overall, our findings indicate a systematic and statistically significant association between cannabis use and symptoms of AD. Frequent use of cannabis and, in particular, its early onset are associated with symptoms of AD in young adults. Because both cannabis use and AD are common events, this association is a serious public health concern. Although the results of the present study suggest a possible causal association between cannabis use and AD in young adults, there is a need for further research to replicate and confirm these findings, examine the direction of association using short-term follow-ups, and examine

which biological and psychosocial factors mediate the apparent effects of cannabis on AD.

Limitations

The present study has some limitations. First, our sample is limited to patients presenting to a public hospital, which may limit the generalizability of the findings. Privately insured patients generally come from more socioeconomically advantaged backgrounds. However, in the present cohort, we found no association between family income, cannabis use, and AD, suggesting that the socioeconomic status of the family does not have an impact on the observed findings. Second, the sequence of follow-up surveys did not allow MUSP to collect information on psychosocial consequences of early onset of cannabis use between the 14- and 21-year follow-ups. This prevented us from further examining the possibility of reverse association between AD and cannabis use during this interval and from ascertaining whether psychosocial consequences of cannabis use are the proximate cause of its association with AD. Studies with the capacity to test this hypothesis should determine whether this is a possible explanation for the relationship.

Third, frequency of use of cannabis and age of initiation were measured at the 21-year follow-up by self-report. However, previous studies have suggested that self-reports of substance use are generally valid and reveal more use than laboratory tests and collateral reports from family members (Buchan et al., 2002). In a 10-year study of the stability of reports of substance use, Shillington et al. (1995) found that cannabis users reported their age at onset of use consistently. In addition, we have not assessed the frequency of use of cannabis before the past month. This raises a possibility that individuals who reported occasional use of cannabis in the past month have had a period of more frequent use previously.

Our primary analyses are based on symptoms of AD as measured by YASR and YSR rather than clinical diagnoses of anxiety and/or depression. To test whether our results were robust, we repeated our analyses for the subsample of participants ($n = 2,475$) for whom we had collected data on affective disorders and total anxiety/panic/phobia disorders at age 21 using the Composite International Diagnostic Interview. The results were consistent with those shown in Table 3, such that early onset and frequent use of cannabis were again

significantly associated with greater risk of affective disorders and total anxiety/panic/phobia disorders. This sensitivity analysis strengthens our findings and suggests that the pattern of cannabis use described here may also be associated with clinically significant anxiety/affective disorders. Future studies with clinical measures of AD should attempt to replicate our findings.

Another limitation is the sizable 33.4% loss to follow-up between the 14- and 21-year surveys. Loss to follow-up may influence our results in two different ways. If the null hypothesis is true, then differential loss to follow-up could not result in an apparent relationship between cannabis and AD. If the alternate hypothesis is true and dropout is differential by either exposure or outcome, however, it is likely that the results presented here underestimate the true association between use of cannabis and AD at age 21. Previous studies indicated that loss to follow-up between the first phase of the study and the 14-year follow-up has been unlikely to affect the findings of MUSP (Mamun et al., 2005). In addition, repeated analyses of the impact of attrition on findings suggest that such impacts are rare (Najman et al., 2005). In any event, the associations evident from analyses weighted by inverse probabilities did not differ from those of the unweighted analyses, suggesting that our results were not substantially affected by attrition bias.

Clinical Implications

Despite some limitations, this study has important implications for prevention of mental health problems. If one accepts that initiation of cannabis use in early adolescence increases the risk of AD in young adults, then a decrease in youth cannabis use may be accompanied by a corresponding decrease in later mental health impairment. From a treatment perspective, early detection of cannabis use may be facilitated if physicians are aware that adolescent use of cannabis may initiate the development of AD in young adults. Screening adolescent patients for cannabis use and intervening early could influence the rate of AD in young adulthood as well as reducing cannabis abuse and dependence. We hope that as information on the vulnerability of cannabis users to significant mental health consequences permeates through high schools, perceptions of harmfulness increase, and use declines.

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Age of Alcohol-Dependence Onset: Associations With Severity of Dependence and Seeking Treatment Ralph W. Hingson, ScD, MPH, Timothy Heeren, PhD, Michael R. Winter, MPH

Objective: We explored whether people who become alcohol dependent at younger ages are more likely to seek alcohol-related help or treatment or experience chronic relapsing dependence. **Methods:** In 2001–2002 the National Institute on Alcohol Abuse and Alcoholism completed a face-to-face interview survey with a multistage probability sample of 43 093 adults aged ≥ 18 , with a response rate of 81%. We focused on 4778 persons diagnosable as alcohol dependent ever in their lives using *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria. Logistic regression examined whether respondents ever sought alcohol-related help or treatment, controlling for respondent demographics, number of dependence symptoms experienced, smoking and illicit drug use, childhood antisocial personality and depression, family history of alcoholism, and age of drinking onset. **Results:** Of persons ever alcohol dependent, 15% were diagnosable before age 18, 47% before age 21, and two thirds before age 25. Twenty-eight percent reported ≥ 2 dependence episodes, 45% experienced an episode exceeding 1 year, and 34% reported 6 or 7 dependence criteria. Relative to those first alcohol dependent at ≥ 30 years, 21% of those ever dependent, the odds of ever seeking help were lower among those first dependent before ages 18, 20, and 25. Yet, persons first dependent at ≤ 25 years had significantly greater odds of experiencing multiple dependence episodes, episodes exceeding 1 year, and more dependence symptoms. Analyses indicated that the previously reported increased odds that persons who start to drink at an early age develop features of chronic relapsing dependence may have resulted from early drinkers being more likely to develop alcohol dependence at younger ages. This, in turn, increased their odds of experiencing multiple and longer episodes of alcohol dependence with more symptoms. **Conclusions:** Adolescents need to be screened and counseled about alcohol, and treatment services should be reinforced by programs and policies to delay age of first alcohol dependence. *Pediatrics* 2006;118:e755–e763.