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Cannabis Use and Earlier Onset of Psychosis

A Systematic Meta-analysis

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Context: A number of studies have found that the use of cannabis and other psychoactive substances is associated with an earlier onset of psychotic illness.

Objective: To establish the extent to which use of cannabis, alcohol, and other psychoactive substances affects the age at onset of psychosis by meta-analysis.

Data Sources: Peer-reviewed publications in English reporting age at onset of psychotic illness in substance-using and non-substance-using groups were located using searches of CINAHL, EMBASE, MEDLINE, PsycINFO, and ISI Web of Science.

Study Selection: Studies in English comparing the age at onset of psychosis in cohorts of patients who use substances with age at onset of psychosis in non-substance-using patients. The searches yielded 443 articles, from which 83 studies met the inclusion criteria.

Data Extraction: Information on study design, study population, and effect size were extracted independently by 2 of us.

Data Synthesis: Meta-analysis found that the age at onset of psychosis for cannabis users was 2.70 years younger (standardized mean difference = -0.414) than for nonusers; for those with broadly defined substance use, the age at onset of psychosis was 2.00 years younger (standardized mean difference = -0.315) than for nonusers. Alcohol use was not associated with a significantly earlier age at onset of psychosis. Differences in the proportion of cannabis users in the substance-using group made a significant contribution to the heterogeneity in the effect sizes between studies, confirming an association between cannabis use and earlier mean age at onset of psychotic illness.

Conclusions: The results of meta-analysis provide evidence for a relationship between cannabis use and earlier onset of psychotic illness, and they support the hypothesis that cannabis use plays a causal role in the development of psychosis in some patients. The results suggest the need for renewed warnings about the potentially harmful effects of cannabis.

Arch Gen Psychiatry.
Published online February 7, 2011.
doi:10.1001/archgenpsychiatry.2011.5

CANNABIS IS THE MOST widely used addictive substance after tobacco and alcohol.¹ The 2009 National Survey on Drug Use and Health reported that more than 16 million Americans use cannabis on a regular basis, most of whom started using cannabis and other drugs during their teenage years.² There is little doubt about the existence of an association between substance use and psychotic illness. National mental health surveys have repeatedly found more substance use, especially cannabis use, among people with a diagnosis of a psychotic disorder.³⁻⁵ There is a high prevalence of substance use among individuals treated in mental health settings,⁶ and patients with schizophrenia are more likely to use substances than members of

the wider community.^{7,8} Prospective birth cohort and population studies suggest that the association between cannabis use and later psychosis might be causal,^{9,10} a conclusion supported by studies showing that cannabis use is associated with an earlier age at onset of psychotic disorders, particularly schizophrenia.¹¹⁻¹⁵

Not all researchers agree that the association between cannabis use and earlier age at onset is causal. Sevy et al¹⁶ argue that the association between cannabis use and earlier age at onset could be explained by demographic variables, including lower socioeconomic status and the proportion of male cannabis users. Wade¹⁷ has suggested that the apparent association between earlier age at onset and cannabis use might simply be owing to older patients with first-episode psychosis being less likely to use cannabis.

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If an association between cannabis use and an earlier age at onset of psychotic disorder were confirmed, the finding would lend support to the possible existence of a causal link between cannabis use and psychosis. This would in turn stimulate research into how cannabis can disrupt brain development and increase the vulnerability to developing psychosis. Evidence already shows that cannabis exposure is associated with a decline in cognitive performance in young people without psychosis¹⁸ and a loss of cortical thickness in early schizophrenia.^{19,20} Other research suggests the presence of a gene \times environment interaction involving cannabis and a functional polymorphism in the enzyme catechol *O*-methyltransferase so that cannabis users with the Val/Val catechol *O*-methyltransferase genotype are at greater risk for developing psychosis²¹ and have a significantly younger age at onset than people with Met/Met or Val/Met alleles.²²

However, attempts to confirm the earlier onset of psychosis among cannabis users found in individual studies have been complicated by the considerable variation in the methods used to examine the association between the age at onset of psychosis and substance use. First, there are differences in the way substances have been examined. Some studies use an omnibus measure of substance use,^{23,24} while others have specifically examined the associations between age at onset and use of alcohol^{25,26} or cannabis.^{27,28} Second, there are differences in the patient populations because some studies include patients with affective psychoses (psychotic depression and mania),^{29,30} whereas others limit samples to patients with a diagnosis of schizophrenia and related disorders.^{31,32} A third area of methodological variation is whether the studies examined substance use at the time of initial presentation to mental health services^{33,34} or later in the course of established psychotic illness.^{35,36} A fourth difference is in the nature of the control group, because some studies use psychotic patients with no reported substance use as controls,¹³ whereas the control groups of other studies include psychotic subjects who used drugs other than the drug under study.²⁷ A fifth point of variation across studies relates to the age range of included patients, because many early-psychosis services only see individuals younger than a certain age, which is a potentially important confounding factor because cannabis use is more prevalent among younger people.¹⁷ Perhaps most importantly, few studies explicitly state whether the substance was being used prior to the onset of psychosis, which makes it difficult to draw causal inferences from a reported association.

We describe a meta-analysis of studies reporting age at onset and substance use to examine the consistency of the association between substance use, in particular cannabis use, and younger age at onset of psychosis.

We considered whether studies of the age at onset of psychosis among substance users and non-substance users would have a greater effect of earlier age at onset of psychosis in studies with a higher proportion of cannabis users compared with studies with a lower proportion of cannabis users. In the language of meta-analysis, we conducted the study with the specific *a priori* hypothesis that between-study heterogeneity in the age at onset of psychosis would be predicted by differences in the proportion of cannabis users in the substance-using groups.

We also examined demographic factors, methodological variations, and indicators of study quality to assess the possibility of a confounding effect arising from the proportion of cannabis users among substance-using groups. Hence, we considered whether between-study heterogeneity in the age at onset of psychosis was associated with the following: (1) the predominance of males in the substance-using groups, because of a potentially confounding statistical association between male sex and earlier age at onset, irrespective of substance use; (2) the proportion of patients with a diagnosis of schizophrenia in the substance-using groups, because of the possibility of a specific causal association of cannabis with schizophrenia rather than with a broader category of psychotic disorders; (3) the use of an upper age limit as a criterion for inclusion in the study, because older subjects might be less likely to use cannabis, spuriously increasing the difference in age at onset of psychotic illness in substance-using groups; (4) the use of age at onset of psychotic symptoms rather than the age at initiation of treatment as the measure of age at onset, because the initiation of treatment is not an accurate marker of the age at onset of the psychotic illness owing to well-recognized treatment delays; (5) the use of systematic methods for diagnosing psychosis and substance use, because higher-quality studies are less likely to have misclassified subjects; (6) whether the studies were conducted during first-episode psychosis or later in the illness, because subjects who commenced or stopped using cannabis after diagnosis could be misclassified; (7) whether the control group contained some subjects who used drugs other than the drug being studied, as was the case in some studies of the effects of use of particular substances such as cannabis, alcohol, and cocaine; (8) the year of publication of the study, because of the possibility that the potency of cannabis has increased over time³⁷; and (9) the reported severity of substance use, including whether the substance use was reported to be heavy or continuous.

METHODS

The methods were based on the guidelines for Meta-analysis of Observational Studies in Epidemiology.³⁸ We used systematic searches of multiple databases; 2 of us independently selected the studies according to our inclusion criteria and then extracted the data. The effect size for age at onset of psychosis was calculated using a random-effects meta-analysis. Sources of between-study heterogeneity, such as those caused by differences in the methods in the included studies, were examined for using meta-regression. The possibility of publication bias was quantified.

SEARCHES

A systematic search of 5 electronic databases (CINAHL, EMBASE, MEDLINE, PsycINFO, and ISI Web of Science) was conducted for publications in English reporting the age at onset of psychotic disorders in cohorts of patients who reported the use of a psychoactive substance (other than tobacco) compared with the age at onset among a control group of patients with psychosis who did not use psychoactive substances (**Figure**). The main search of the first 4 databases was not limited by the inclusion of "age of onset" or "age" among the search terms because most of the relevant papers could not be located using those terms. More-

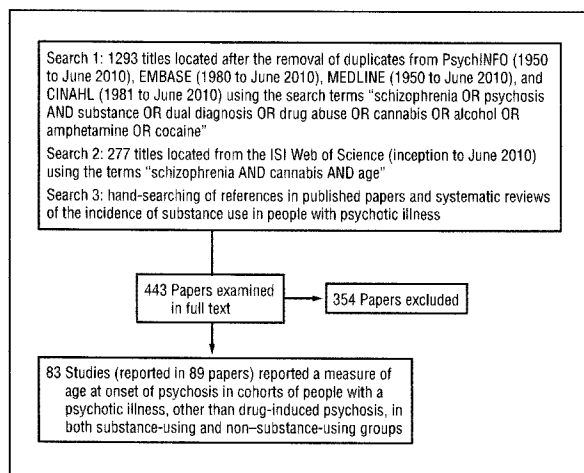


Figure. Flowchart of search strategies and results.

over, the abstracts of papers yielded by electronic searches proved to be an unreliable guide to the presence of age-at-onset data. Hence, any paper considered likely to contain demographic data about cohorts of substance-using and non-substance-using patients with psychosis was examined in full text by 2 of us (M.L. and S.S.), and the references of the included studies and those of previous reviews of the association between cannabis and psychosis were hand-searched for further relevant studies.

The results of 83 studies were included in the meta-analysis, which incorporated 8 studies that met the inclusion criteria after further data needed for meta-analysis were provided by the primary researchers. Two authors of similar studies were unable to provide the additional data and their studies were not included. No unpublished studies or studies published from non-peer-reviewed sources were considered. Studies were included if they reported the mean and standard deviation (or other effect size data) of age at onset of psychotic illness in a substance-using group and a non-substance-using control group. There were not enough studies reporting a temporal relationship between the onset of substance use and the onset of psychosis to include this in the meta-analysis.

DEFINITION OF SUBSTANCE USE

The meta-analyzed studies used a range of definitions of substance use. In all of the studies, the degree of substance use was considered to be clinically significant; in many studies, the diagnosis of a substance use disorder was the threshold for inclusion in the substance-using group. Where possible, the contribution to between-study heterogeneity of heavy or more continuous substance use and less heavy or discontinued substance use was examined. However, the random-effects meta-analysis used in this study only required that thresholds are consistently applied within studies and allows for differences in sampling and measurement between studies, such as differences in the threshold for inclusion in the substance-using group.

TOBACCO USE

No study included tobacco use in its definition of substance use. There were likely to have been tobacco users in both the substance-using and non-substance-using groups in every included study. Hence, the extent to which tobacco use was associated with other forms of substance use or the extent to which tobacco use might be associated with the age at onset of psychosis could not be addressed using this data set. Few studies reported the age at onset of psychosis for tobacco users and nonusers.^{11,39}

DATA EXTRACTION

The data were independently extracted by 2 of us (M.L. and S.S.). The origins of the data were not blinded for data extraction because we did not believe this information would be a source of bias. Twelve differences in more than 2000 data points were resolved by a joint examination of the papers. The following data were extracted:

- The substances examined, the number of substance-using and non-substance-using patients, and either the mean age and standard deviation of the substance-using and non-substance-using groups or other data such as an effect size suitable for meta-analysis.
- The proportion of cannabis-using patients in the substance-using group.
- The proportion of patients with a schizophrenia-related psychosis.
- The proportion of males in the substance-using and non-substance-using groups.
- The preponderance of male patients in the substance-using group, estimated as the ratio of the proportion of males in the substance-using and control groups.
- An inclusion criterion of being aged 45 years or younger.
- Whether age at onset of psychosis referred to the age at the time of onset of psychotic symptoms or the age at the first treatment for psychosis.
- Whether systematic measures such as structured interviews were used to diagnose both substance use and psychotic disorders.
- Whether the study was conducted exclusively among patients with first-episode psychosis.
- Whether all substance-using subjects were excluded from the control group in studies examining age at onset associated with specific substances.
- The year the study was published.
- Whether the substance use was thought to be heavy and whether the substance use continued after the diagnosis of psychosis.

META-ANALYSIS

Standardized mean differences and meta-analytically estimated differences in means (in years) were calculated using Comprehensive Meta-analysis version 2 software (Biostat, Inc, Englewood, New Jersey). Standardized mean difference (the difference between 2 normalized means) was used as the main outcome measure because it is not affected by variation in mean age between studies and can be calculated from a wide variety of effect size data.

Substance use and age were both regarded as positive factors, so that an effect size with a larger negative value indicated an earlier age at onset in the substance-using group when compared with the controls. The between-study heterogeneity in effect sizes was examined using I^2 and Q-value statistics. Meta-regression was used to examine the predictors of heterogeneity with a method-of-moments model using Comprehensive Meta-analysis software. Variables found to contribute significantly to the between-study heterogeneity were included in a multivariate meta-regression that was carried out in Intercooled Stata version 9.1 software (StataCorp LP, College Station, Texas) using the *metareg* procedure. The within-studies component of variance was derived from the calculated variation in the standardized mean difference in age at onset. The between-studies component of variance was estimated by the restricted maximum likelihood procedure. Standardized mean differences were used as the effect size measure, but point estimates in years are also reported for ease of interpretation.

Table 1. Meta-analysis of Substance Use and Age at Onset of Psychosis Grouped by Substance, Sex, and Severity of Substance Use

Group	Samples No.	Effect Size, y	Effect Size, Standardized Mean Difference				Between-Sample Heterogeneity	Between-Group Heterogeneity
			Point Estimate	SE	Variance	95% CI		
All studies defined by substance use type								
Alcohol use	22	-0.28	-0.038	0.081	0.007	-0.196 to 0.120	Q=495; df(Q)=130; I ² =78.1 P(Q)≤.001; P(Q)=.001	Q=14.52; df(Q)=2; P(Q)=.001
Cannabis use ^a	41 ^a	-2.70	-0.414	0.058	0.003	-0.526 to -0.301		
Substance use ^b	68 ^b	-2.00	-0.315	0.046	0.002	-0.405 to -0.225		
Overall	131	-1.73	-0.264	0.096	0.009	-0.453 to -0.075		
Studies reporting groups by sex								
Females	13	-3.40	-0.365	0.131	0.017	-0.622 to -0.108	Q=276; df(Q)=36; I ² =86.9 P(Q)≤.001; P(Q)=.81	Q=0.1; df(Q)=1; P(Q)=.81
Males	24	-1.87	-0.325	0.096	0.009	-0.513 to -0.138		
Studies reporting groups of heavy or continued users vs lighter or discontinuing users								
Lighter or discontinued use	10	-2.07	-0.301	0.113	0.013	-0.522 to -0.080	Q=33.7; df(Q)=19; I ² =43.7 P(Q)=.02; P(Q)=.42	Q=0.6; df(Q)=1; P(Q)=.42
Heavy or continued use	10	-2.72	-0.428	0.110	0.012	-0.644 to -0.211		

Abbreviation: CI, confidence interval.

^aIncludes 1 study of cocaine users, all of whom also used cannabis.

^bIncludes 3 studies of cocaine users.

Subgroup analysis was performed using the subset of studies reporting data for males and females separately and for studies reporting data both for heavy or ongoing substance use and for lighter and infrequent or discontinued substance use. A random-effects model was used in all analyses because of the differences in methods and patient groups between the studies.

PUBLICATION BIAS

Three methods were used to investigate publication bias. First, a funnel (Egger) plot of the effect size vs the variance was inspected⁴⁰ for the presence of smaller studies with a large effect size indicating an earlier age at onset associated with substance use. Second, the classic fail-safe N was used to estimate the number of hypothetical missing studies with an effect size of 0 that would be required to return to $P > .05$. Third, using the trim and fill method by Duval and Tweedie,⁴¹ we examined the possible effect of hypothetically missing studies on the pooled estimate of the standardized mean difference. The possibility of bias introduced by the exclusion of non-English-language papers was not examined.

RESULTS

SEARCHES

We found 83 studies containing a total of 131 samples of the mean age at onset of psychosis in substance-using and non-substance-using individuals with psychotic disorders (Figure, eTable, eFigure, and eReferences [http://www.archgenpsychiatry.com]). The 131 included samples comprised 8167 substance-using patients (mean [SD], 62.4 [69.0] substance-using patients per sample) and 14 352 non-substance-using patients (mean [SD], 109.6 [137.3] non-substance-using patients per sample).

PUBLICATION BIAS

There was no statistical evidence of publication bias. The funnel plot was symmetrical, indicating that there was no statistical evidence of missing studies. No study was iden-

tified by the trim and fill method; therefore, no adjustment of the point estimate was made. The classic fail-safe N test found that 1098 studies of a similar size with an effect size of 0 would be needed to return the study to $P > .05$.

META-ANALYSIS

Meta-analysis of age at onset of psychosis revealed that the age at onset was 2.70 years earlier among samples of cannabis users ($z = -7.18$; $P < .001$) and was 2.00 years earlier in samples with unspecified substance use compared with non-substance-using controls ($z = -6.87$; $P < .001$) (Table 1). Alcohol-using samples were nonsignificantly younger than the control groups (-0.28 years; $z = -0.47$; $P = .64$). Overall, the mean age of the substance-using groups in the 131 samples was 1.73 years younger than in the control groups ($z = -2.74$; $P = .006$). Subgroup analyses demonstrated that the pooled estimate of the effect size indicating earlier age at onset among substance users was greater among women (-3.40 years) than among men (-1.87 years), but this difference was not statistically significant (Table 1). The pooled estimate of the effect size indicating earlier age at onset was greater in heavy or continuous substance users (-2.72 years) than in subjects who were rated as having lighter substance use or who had stopped use (-2.07 years), but this difference between groups was not statistically significant (Table 1).

META-REGRESSION AND MULTIPLE META-REGRESSION

First, a higher proportion of cannabis users among the substance-using groups was associated with a greater negative effect size, indicating an earlier mean age at onset of psychosis. This could be seen in the group of studies that specifically examined cannabis use and was also demonstrated by meta-regression (Table 2) and multiple meta-regression (Table 2). Second, meta-regression suggested that an overrepresentation of males in the substance-

Table 2. Meta-regression and Multiple Meta-regression of Factors Associated With Heterogeneity in the Effect Size of Substance Use on the Age at Onset of Psychosis

Factor	Samples, No. ^a	Point Estimate of Slope	SE of Slope	95% CI of Slope	Z Value	P Value	τ^2
Meta-regression of sample characteristics							
Proportion using cannabis in substance-using group	114	-0.004	0.001	-0.006 to -0.002	-3.34	<.001	0.088
Ratio of proportion of males in substance-using and control groups	102	-0.240	0.117	-0.469 to -0.011	-2.05	.04	0.089
Proportion of all subjects with schizophrenia	119	0.002	0.002	-0.002 to 0.005	0.83	.41	0.113
Meta-regression of methodological and quality characteristics							
Upper limit of age ≥ 45 y at presentation	26/131	-0.242	0.082	-0.402 to -0.081	-2.96	.003	0.102
Some substance users in control group	55/131	0.020	0.071	-0.118 to 0.158	-0.28	.77	0.111
Conducted at time of first episode of psychosis	61/131	-0.067	0.068	-0.202 to 0.068	-0.97	.33	0.107
Defined onset as time of initial treatment	44/131	-0.023	0.075	-0.170 to 0.125	-0.30	.76	0.111
Systematic measure for diagnosis and substance use	87/131	0.038	0.074	-0.106 to 0.182	0.52	.60	0.111
Year of publication of studies	131	0.003	0.005	-0.007 to 0.014	0.66	.51	0.111
Multiple meta-regression of factors found to be associated with between-study heterogeneity by meta-regression							
Ratio of proportion of males in substance-using and control groups		-0.253	0.142	-0.532 to 0.025	-1.78	.08	0.078
Proportion of cannabis users	87 ^b	-0.004	0.001	-0.006 to -0.001	-2.83	.006	
Age ≥ 45 y at presentation		-0.216	0.089	-0.390 to -0.025	-2.44	.02	
Constant		0.422	0.210	0.010 to 0.834	2.01	.04	

Abbreviation: CI, confidence interval.

^aSome variables had a lower number of samples owing to missing data.

^bNumber of samples reporting these 3 variables.

using groups was associated with a greater negative effect size, indicating an earlier mean age at onset of psychosis. Third, meta-regression indicated that samples that included subjects older than 45 years also had an earlier age at onset of psychosis associated with substance use when compared with the group of studies that included younger patients only. Multiple meta-regression found that cannabis use and the sample age range made independent contributions to the observed heterogeneity in effect sizes, while a trend toward a higher ratio of males contributing to a larger negative effect size was not significant.

Other variables that did not contribute to the heterogeneity of effect size of substance use on age at onset included the following: the proportion of patients with schizophrenia and related nonaffective psychotic disorders; whether the study used systematic measures for diagnosis; whether the study was conducted in patients with first-episode psychosis; whether the control groups might have included some users of other substances; whether the onset of psychosis was defined by the onset of symptoms or the date of initial treatment; and the year of publication of the study.

COMMENT

We found that the use of cannabis and other illicit substances was associated with an earlier age at onset of psychotic disorders. In contrast, alcohol use alone did not appear to be significantly associated with a younger age at onset of psychosis. With regard to our a priori hypothesis, we found that a higher proportion of cannabis users in the substance-using groups significantly contributed to the heterogeneity in the effect size, indicating an earlier mean age at onset of psychosis in samples with more cannabis users.

With respect to the demographic and clinical factors, we found that an increased proportion of males in the substance-using groups relative to control groups significantly contributed to the heterogeneity in the effect size, but this was not independent of the association between cannabis use and age at onset when examined with multiple meta-regression. Hence, there was no evidence that the association between male sex and earlier age at onset of psychosis was the reason for the association between cannabis use and an earlier age at onset. Furthermore, the proportion of patients with schizophrenia did not significantly contribute to the heterogeneity in the effect size, suggesting that a possible association between young age, cannabis use, and a diagnosis of schizophrenia rather than affective psychosis could not explain the association between cannabis use and an earlier age at onset of psychosis.

The methods used in this study allowed us to examine whether the observed association between substance use and earlier age at onset might be a result of substance use being more common among younger people, including those with schizophrenia, which has been a criticism of individual studies.¹⁷ We found that the use of an upper age limit as an inclusion criterion significantly contributed to the heterogeneity in the effect size, suggesting that the presence of a greater number of older non-cannabis users in a sample might spuriously contribute to the difference in mean age between the substance-using and non-substance-using groups. However, the finding of an association between the proportion of cannabis users and earlier age at onset was statistically independent of age inclusion criteria. This suggests that some of the observed difference in the age at onset of psychosis in substance-using and non-substance-using groups might well be because of the association between young age and substance abuse

but that the observed effect cannot be wholly explained by an association between young age and cannabis use.

No other methodological or study quality issues that we examined were associated with between-study heterogeneity in effect size for age at onset of psychosis. These included measures of the severity of substance use, how the onset of psychosis was measured, whether structured instruments were used to make the diagnoses of psychosis and substance abuse, whether the study only included patients with first-episode psychosis, the possibility that users of other substances were included in the control groups, and the year the study was conducted. Hence, it was unlikely that variations in the methods or the quality of studies greatly affected the main finding of a significantly younger age at onset of psychosis among substance users, especially users of cannabis.

One limitation of this study was the absence of data to enable us to examine the extent to which tobacco use is associated with an earlier age at onset, because insufficient tobacco use data were available for meta-analysis. It is conceivable that the apparent association between cannabis and psychosis is in fact related to a neurotoxin in tobacco, which is almost always mixed with cannabis. However, this is a weakness of all naturalistic studies of cannabis and psychosis, and tobacco use by itself has not been considered to be a factor contributing to exacerbations of psychosis in people with established illness.

A further limitation of this form of study is the possibility of ecological fallacy in meta-analyses that do not examine data from individual subjects.⁴² An example might be if the non-cannabis-using patients in the substance-using groups had the youngest age at onset. A future study using individual patient data could clarify the influence of tobacco use and confirm that the finding was not due to an ecological fallacy.⁴²

A number of hypotheses have been proposed to explain the association between cannabis use and schizophrenia, including the following: (1) that cannabis use is a causal factor for schizophrenia; (2) that cannabis use precipitates psychosis in vulnerable people; (3) that cannabis use exacerbates symptoms of schizophrenia; and (4) that people with schizophrenia are more likely to use cannabis.⁴³ This study lends weight to the view that cannabis use precipitates schizophrenia and other psychotic disorders, perhaps by an interaction between genetic and environmental factors as has been suggested for cannabis and catechol *O*-methyltransferase^{21,22} or by disrupting brain development, especially during the important neurological maturation that takes place during adolescence.⁴⁴ Our findings do not support the view that people with a propensity to develop psychosis at a young age are simply more likely to use all substances, because alcohol use was not associated with a younger age at onset. However, the possibility that those who are destined to develop psychosis at an early age are more prone to use substances such as tobacco could be examined in future studies.

The results of this systematic review and meta-analysis represent strong scientific evidence for an association between substance use, particularly the use of cannabis, and an earlier age at onset of psychotic illnesses. The association between the extent of cannabis use in the substance-using group and the effect size as well as the

weaker association between earlier age at onset and alcohol use support the hypothesis that cannabis use is a causal factor in psychotic disorders. The finding raises the important questions of whether cannabis and other substances can trigger psychosis by direct neurotoxic effects, by alterations in dopamine activity, or by other changes in neurotransmission and the extent to which any adverse effects on the brain are reversible.^{45,46} These results confirm the need for further neurobiological research to find the mechanisms by which cannabis use triggers or brings forward psychotic illness.

The results of this study provide strong evidence that reducing cannabis use could delay or even prevent some cases of psychosis. Reducing the use of cannabis could be one of the few ways of altering the outcome of the illness because earlier onset of schizophrenia is associated with a worse prognosis and because other factors associated with age at onset, such as family history and sex, cannot be changed.⁴⁷ Building on several decades of research, this finding is an important breakthrough in our understanding of the relationship between cannabis use and psychosis. It raises the question of whether those substance users would still have gone on to develop psychosis a few years later. However, even if the onset of psychosis were inevitable, an extra 2 or 3 years of psychosis-free functioning could allow many patients to achieve the important developmental milestones of late adolescence and early adulthood that could lower the long-term disability arising from psychotic disorders. The results of this study confirm the need for a renewed public health warning about the potential for cannabis use to bring on psychotic illness.

Submitted for Publication: October 11, 2010; final revision received November 9, 2010; accepted December 1, 2010.

Published Online: February 7, 2011. doi:10.1001/archgenpsychiatry.2011.5

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Authors Contributions: Dr Large had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Financial Disclosure: None reported.

Online-Only Material: The eTable, eFigure, and eReferences are available at <http://www.archgenpsychiatry.com>.

Additional Contributions: The following authors and their associates provided unpublished data or other information about their studies: Evelyn Bromet, PhD,

Jason Carr, PhD, Vaughn Carr, MD, Ian Fowler, MB BS, Alan Green, MD, David Kavanagh, DPhil, Roman Kotov, PhD, Martin Hambrecht, PhD, Marie-Odile Krebs, PhD, Rodolfo Mazzoncini, PhD, Jonathan Rabinowitz, PhD, Christopher Tennant, MD, Darryl Wade, PhD, and Geoffrey Waghorn, PhD. Vera Morgan, PhD, provided data reported by Kavanagh et al (*Schizophr Res*. 2004;66[2-3]:115-124) from the Confidentialised Unit Record File for the Australian National Low Prevalence (Psychotic) Disorders Study 1997-98. Peter Arnold, MBBCh, assisted in the preparation of the manuscript.

REFERENCES

- Degenhardt L, Chiu WT, Sampson N, Kessler RC, Anthony JC, Angermeyer M, Bruffaerts R, de Girolamo G, Gureje O, Huang Y, Karam A, Kostyuchenko S, Lepine JP, Mora ME, Neumarck Y, Ormel JH, Pinto-Meza A, Posada-Villa J, Stein DJ, Takeshima T, Wells JE. Toward a global view of alcohol, tobacco, cannabis, and cocaine use: findings from the WHO World Mental Health Surveys. *PLoS Med*. 2008;5(7):e141.
- US Department of Health and Human Services. Results From the 2009 National Survey on Drug Use and Health, Volume I: Summary of National Findings: 1.1, Summary of NSDUH. <http://www.oas.samhsa.gov/NSDUH/2k9NSDUH/2k9Results.htm#1.1>. Accessed October 27, 2010.
- McMillan KA, Enns MW, Cox BJ, Sareen J. Comorbidity of Axis I and II mental disorders with schizophrenia and psychotic disorders. *Can J Psychiatry*. 2009;54(7):477-486.
- Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, Goodwin FK. Comorbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiologic Catchment Area (ECA) Study. *JAMA*. 1990;264(19):2511-2518.
- Kavanagh DJ, Waghorn G, Jenner L, Chant DC, Carr V, Evans M, Hemman H, Jablensky A, McGrath JJ. Demographic and clinical correlates of comorbid substance use disorders in psychosis. *Schizophr Res*. 2004;66(2-3):115-124.
- Carrà G, Johnson S. Variations in rates of comorbid substance use in psychosis between mental health settings and geographical areas in the UK. *Soc Psychiatr Psychiatr Epidemiol*. 2009;44(6):429-447.
- Koskinen J, Löhönen J, Koponen H, Isohanni M, Miettunen J. Prevalence of alcohol use disorders in schizophrenia. *Acta Psychiatr Scand*. 2009;120(2):85-96.
- Koskinen J, Löhönen J, Koponen H, Isohanni M, Miettunen J. Rate of cannabis use disorders in clinical samples of patients with schizophrenia: a meta-analysis. *Schizophr Bull*. 2010;36(6):1115-1130.
- Henquet C, Murray R, Linszen D, van Os J. The environment and schizophrenia: the role of cannabis use. *Schizophr Bull*. 2005;31(3):608-612.
- Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, Lewis G. Cannabis use and risk of psychotic or affective mental health outcomes. *Lancet*. 2007;370(9584):319-328.
- Compton MT, Kelley ME, Ramsay CE, Pringle M, Goulding SM, Esterberg ML, Stewart T, Walker EF. Association of pre-onset cannabis, alcohol, and tobacco use with age at onset of prodrome and age at onset of psychosis in first-episode patients. *Am J Psychiatry*. 2009;166(11):1251-1257.
- Rabinowitz J, Bromet EJ, Lavelle J, Carlson G, Kovasznay B, Schwartz JE. Prevalence and severity of substance use disorders and onset of psychosis in first-admission psychotic patients. *Psychol Med*. 1998;28(6):1411-1419.
- Hambrecht M, Häfner H. Substance abuse and the onset of schizophrenia. *Biol Psychiatry*. 1996;40(11):1155-1163.
- Veen ND, Selten JP, van der Tweel I, Feller WG, Hoek HW, Kahn RS. Cannabis use and age at onset of schizophrenia. *Am J Psychiatry*. 2004;161(3):501-506.
- González-Pinto A, Vega P, Ibáñez B, Mosquera F, Barbeito S, Gutiérrez M, Ruiz de Azúa S, Ruiz I, Vieta E. Impact of cannabis and other drugs on age at onset of psychosis. *J Clin Psychiatry*. 2008;69(8):1210-1216.
- Sevy S, Robinson DG, Napolitano B, Patel RC, Gunduz-Bruce H, Miller R, McCormack J, Lorell BS, Kane J. Are cannabis use disorders associated with an earlier age at onset of psychosis? *Schizophr Res*. 2010;120(1-3):101-107.
- Wade D. Cannabis use and schizophrenia. *Am J Psychiatry*. 2005;162(2):401-402, author reply 402.
- Fried PA, Watkinson B, Gray R. Neurocognitive consequences of marijuana: a comparison with pre-drug performance. *Neurotoxicol Teratol*. 2005;27(2):231-239.
- Habets P, Marcellis M, Gronenschild E, Drukker M, Os JV, GROUP. Reduced cortical thickness as an outcome of differential sensitivity to environmental risks in schizophrenia [published online October 15, 2010]. *Biol Psychiatry*. doi:10.1016/j.biopsych.2010.08.010.
- Rais M, van Haren NE, Cahn W, Schnack HG, Lepage C, Collins L, Evans AC, Hulshoff Pol HE, Kahn RS. Cannabis use and progressive cortical thickness loss in areas rich in CB1 receptors during the first five years of schizophrenia. *Eur Neuropsychopharmacol*. 2010;20(12):855-865.
- Caspi A, Moffitt TE, Cannon M, McClay J, Murray R, Harrington H, Taylor A, Arseneault L, Williams B, Braithwaite A, Poulton R, Craig IW. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene. *Biol Psychiatry*. 2005;57(10):1117-1127.
- Pelayo-Terán JM, Pérez-Iglesias R, Mata I, Carrasco-Marín E, Vázquez-Barquero JL, Crespo-Facorro B. Catechol-O-Methyltransferase (COMT) Val158Met variations and cannabis use in first-episode non-affective psychosis: clinical-onset implications. *Psychiatry Res*. 2010;179(3):291-296.
- Addington J, Addington D. Effect of substance misuse in early psychosis. *Br J Psychiatry Suppl*. 1998;172(33):134-136.
- Barnes TR, Mutsaers SH, Hutton SB, Watt HC, Joyce EM. Comorbid substance use and age at onset of schizophrenia. *Br J Psychiatry*. 2006;188:237-242.
- Akvardar Y, Tumuklu M, Akdede BB, Ulas H, Kitis A, Alptekin K. Substance use among patients with schizophrenia in a university hospital. *Bull Clin Psychopharmacol*. 2004;14(4):191-197.
- Tsuang JW, Lohr JB. Effects of alcohol on symptoms in alcoholic and nonalcoholic patients with schizophrenia. *Hosp Community Psychiatry*. 1994;45(12):1229-1230.
- Arendt M, Rosenberg R, Foldager L, Perto G, Munk-Jørgensen P. Cannabis-induced psychosis and subsequent schizophrenia-spectrum disorders: follow-up study of 535 incident cases. *Br J Psychiatry*. 2005;187:510-515.
- Bersani G, Orlandi V, Kotzalidis GD, Panzeri P. Cannabis and schizophrenia: impact on onset, course, psychopathology and outcomes. *Eur Arch Psychiatry Clin Neurosci*. 2002;252(2):86-92.
- Carr JAR, Norman RGM, Manchanda R. Sociodemographic and clinical characteristics of patients presenting with first-episode psychotic and concurrent substance misuse. *Early Interv Psychiatry*. 2009;3(1):75-79. doi:10.1111/j.1751-7893.2008.00100.x.
- Mazzoncini R, Donoghue K, Hart J, Morgan C, Doody GA, Dazzan P, Jones PB, Morgan K, Murray RM, Fearon P. Illicit substance use and its correlates in first episode psychosis. *Acta Psychiatr Scand*. 2010;121(5):351-358.
- Modestin J, Gladen CJ, Christen S. A comparative study on schizophrenic patients with dual diagnosis. *J Addict Dis*. 2001;20(4):41-51.
- Sevy S, Robinson DG, Holloway S, Alvir JM, Woerner MG, Bilder R, Goldman R, Lieberman J, Kane J. Correlates of substance misuse in patients with first-episode schizophrenia and schizoaffective disorder. *Acta Psychiatr Scand*. 2001;104(5):367-374.
- Van Mastrigt S, Addington J, Addington D. Substance misuse at presentation to an early psychosis program. *Soc Psychiatry Psychiatr Epidemiol*. 2004;39(1):69-72.
- Turkington A, Mulholland CC, Rushe TM, Anderson R, McCaul R, Barrett SL, Barr RS, Cooper SJ. Impact of persistent substance misuse on 1-year outcome in first-episode psychosis. *Br J Psychiatry*. 2009;195(3):242-248.
- Buckley P, Thompson P, Way L, Meltzer HY. Substance abuse among patients with treatment-resistant schizophrenia. *Am J Psychiatry*. 1994;151(3):385-389.
- Cantor-Graae E, Nordström LG, McNeil TF. Substance abuse in schizophrenia: a review of the literature and a study of correlates in Sweden. *Schizophr Res*. 2001;48(1):69-82.
- Eisohly MA, Ross SA, Mehmedic Z, Ararat R, Yi B, Banahan BF III. Potency trends of delta9-THC and other cannabinoids in confiscated marijuana from 1980-1997. *J Forensic Sci*. 2000;45(1):24-30.
- Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting: Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283(15):2008-2012.
- Wade D, Harrigan S, Edwards J, Burgess PM, Whelan G, McGorry PD. Course of substance misuse and daily tobacco use in first-episode psychosis. *Schizophr Res*. 2006;81(2-3):145-150.
- Cooper H, Hedges L. *Handbook of Research Synthesis*. New York, NY: Russell Sage Foundation; 1994.
- Duval S, Tweedie R. Trim and fill. *Biometrics*. 2000;56(2):455-463.
- Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ*. 2010;340:c221.
- Degenhardt L, Hall W, Lynskey M. Testing hypotheses about the relationship between cannabis use and psychosis. *Drug Alcohol Depend*. 2003;71(1):37-48.
- Trezza V, Cuomo V, Vanderschuren LJ. Cannabis and the developing brain: insights from behavior. *Eur J Pharmacol*. 2008;585(2-3):441-452.
- Luzi S, Morrison PD, Powell J, di Forti M, Murray RM. What is the mechanism whereby cannabis use increases risk of psychosis? *Neurotox Res*. 2008;14(2-3):105-112.
- Freedman R. Cannabis, inhibitory neurons, and the progressive course of schizophrenia. *Am J Psychiatry*. 2008;165(4):416-419.
- Kuehn BM. Early interventions for schizophrenia aim to improve treatment outcomes. *JAMA*. 2010;304(2):139-140, 145.