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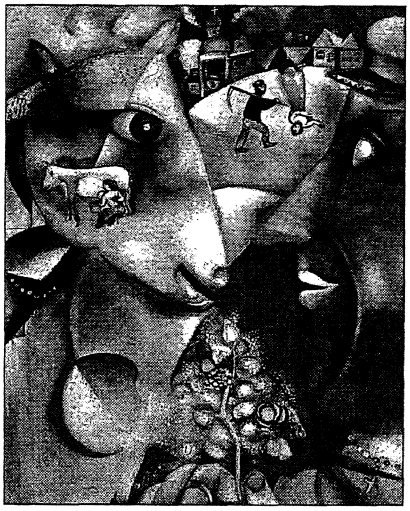

Marc Chagall (1887-1985), *I and the Village*, 1911, French.

Letters

120 Years of CONTINUOUS PUBLICATION

EDITOR
Catherine D. DeAngelis, MD, MPH

July 16, 2003

ORIGINAL CONTRIBUTIONS

CARING FOR THE CRITICALLY ILL PATIENT

EDITORIALS

CLINICIAN'S CORNER

CLINICAL CROSSROADS

Early Exposure to Marijuana and Risk of Later Drug Use

To the Editor: Dr Lynskey and colleagues[1] concluded that early cannabis use is associated with an increased risk for later use and dependence on other drugs. Although the authors used both monozygotic and dizygotic same-sex twins to ensure similar environmental influences, we are concerned that the sample may not be representative of the population, as there was an unusually high prevalence of alcohol dependence in both cannabis users and their co-twin controls compared with that of the general population.[2,3] Early cannabis users in the study of Lynskey et al had a 42.8% prevalence of alcohol dependence, whereas their co-twin controls had a prevalence of 29.6%. By contrast, the prevalence of alcohol abuse among Australian adults has been reported to be about 6.5%,[2,4] with a 4.1% prevalence of alcohol dependence.[2] About 8.3% of Australians aged 14 years and older report daily alcohol use.[5] Similarly, the prevalence of alcohol dependence in the United States has been estimated to be about 6% of men and 2% of women.[3]

Joshua G. Schier, MD
Lewis S. Nelson, MD
Robert S. Hoffman, MD
NYC Poison Control Center
New York, NY

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To the Editor: Dr Lynskey and colleagues[1] used a matched cohort design to study the association between cannabis use by the age of 17 years with drug use later in life. Twins who had used cannabis by the age of 17 years were matched with their sibling who had not used cannabis by that age. This design eliminates possible confounding by any shared genetic and environmental factors. The authors estimated odds ratios (ORs) using conditional logistic regression.

Odds ratios tend to overestimate the magnitude of risk ratios when outcome events are common.[2] In Table 2 of the study by Lynskey et al, it appears that among 311 pairs of twins, both siblings went on to use cocaine in 61 pairs; only the cannabis user went on to use cocaine in 88 pairs; only the twin who had not used cannabis went on to use cocaine in 21 pairs; and neither twin used cocaine in the remaining 141 pairs. Accounting for the matching, the OR for later cocaine use for study subjects who used cannabis by the age of 17 years, compared with their twins, was $88/21 = 4.19$, which was reported by the authors. The matched-pair risk ratio, which was not reported, was much smaller and closer to 1.0: $(61+88)/(61+21) = 1.82$. For the outcomes of sedative use, hallucinogen use, and opioid use, the matched-pair ORs were 2.83, 5.15, and 2.57, whereas the risk ratios were 2.27, 1.96, and 2.10.

Odds ratios can be mistaken for risk ratios, and this may result in significant misunderstandings of study results.[3] Odds ratios that do not approximate risk ratios cannot be used, without other information, to estimate the proportion of cases that can be attributed to, or prevented by, an exposure. However, a matched cohort design can be used to estimate adjusted risk ratios from matched-pair data using conditional Poisson regression or Cox proportional hazards regression.[4,5] These methods are available in several commercial software packages.

Peter Cummings, MD, MPH
Department of Epidemiology
Harborview Injury Prevention and Research Center
University of Washington
Seattle

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To the Editor: Dr Lynskey and colleagues[1] interpreted their data as providing evidence that cannabis use caused subsequent drug problems through a "gateway" effect.

This study, however, may have been subject to various biases that would negate this interpretation. For example, drug use and problems were measured via uncorroborated self-

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Letters Section Editor: Stephen J. Lurie, MD, PhD, Senior Editor.

report, which can be unreliable.[2] Different individuals, due mainly to different perceptions of social desirability, may tend to either underreport or overreport their experience of drug use and drug problems. Such reporting tendency would generate a spurious association between use of and problems with one drug and use of and problems with another. The importance of the issue of reporting bias may have been generally underestimated in observational epidemiology.[3]

There are also possible sources of confounding. Both early cannabis use and other drug problems may share common antecedents, and the apparent association between them may simply reflect this. Although the authors claim to have overcome this problem, their argument rests on the assumption that same sex co-twins have the same exposure to determinants of drug use. Clearly, this is not the case in a subsample defined by the fact that they were *discordant* for cannabis use by the age of 17 years. The same factors that caused this discordance could have confounded the association between early cannabis use and other drug problems. Because adjustment for the limited range of possible confounding factors measured had little influence on the estimates, this suggests either that important factors were unmeasured or that correlated covariates were measured imprecisely. The limitations of statistical adjustment in this latter situation have been described by Davey Smith and Phillips.[4]

Finally, chronic cannabis use seems unlikely to be harmless since many users apparently smoke it with tobacco.[5] There appears little reason, however, to add "gateway" effects to the list of possible harms of cannabis.

John Macleod, PhD
Department of Primary Care and General Practice
University of Birmingham
Birmingham, England

Matthew Hickman, PhD
Centre for Research on Drugs and Health Behaviour
Imperial College of Science, Technology and Medicine
London, England

George Davey Smith, DSc
Department of Social Medicine
University of Bristol
Bristol, England

1. Lynskey MT, Heath AC, Bucholz KK, Slutske WS, Madden PAF, Nelson EC, et al. Escalation of drug use in early-onset cannabis users vs co-twin controls. *JAMA*. 2003;289:427-433.
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To the Editor: In her Editorial about the possible causal mechanisms of drug addiction, Dr Kandel[1] did not discuss the risk associated with prenatal administration of opiates or sedatives. Several studies[2-4] have found that administration of these drugs during labor is a risk factor for later addiction in adolescence or adulthood. Not only have these studies found a dose-response relationship between drug exposure and subsequent risk of drug addiction, but also have the advantage that the perinatal drug exposure is limited to a few hours during birth. This restricts the range of confounding factors (eg, socioeconomic status or residential environment[5,6]) that can possibly moderate this long-term effect. Since any drug administered prenatally would be expected to cross the placenta about equally to twin fetuses irrespective of whether they are monozygotic or dizygotic twins, such an explanation is consistent with the observation that no differences were found between these 2 categories of twins in the recent study by Lynskey et al.[7] Epidemiological studies that do not assess or control for proximate factors on subsequent drug addiction may have a limited ability to examine the effects of other causal factors occurring later in the drug addict's life.

K. J. S. Anand, MBBS, DPhil
Arkansas Children's Hospital
Little Rock

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In Reply: We disagree with Dr Schier and colleagues that the high rate of alcohol dependence in our sample invaliditates our conclusions. First, we reported lifetime prevalence, whereas previous work only presented 12-month estimates.[1] Furthermore, the rates we reported were for twin pairs discordant for early cannabis use. Early substance use is associated with increased risks for substance dependence and thus elevated rates of alcohol (and other) drug dependence would be expected among early cannabis users. Because a large component of the association between early use and later risks of dependence likely arises from genetic and shared environmental factors preceding cannabis use, and because co-twins of early users would have been exposed to these same risk factors, they would also be expected to have elevated rates of alcohol dependence. Thus, the elevated rate of alcohol dependence reflects and reinforces our rationale for conducting the study. Finally, it demonstrates that a large component of previously observed associations between early cannabis use and later drug use can be attributed to heritable and shared environmental factors. In this respect, it is noteworthy that the strength of the associations that we report is substantially lower than those reported by previous studies that have not included such stringent control.

Dr Cummings highlights the risks of possible misinterpretation of ORs. However, as he demonstrates, it is possible for readers to calculate risk ratios (RRs) from the data we presented and, regardless of whether ORs or RRs are reported, the substantive conclusions of our results remain unchanged.

Dr Macleod and colleagues suggest that our results are an artifact of the unreliability of self-report. However, despite the limitations of self-report, previous research has consistently concluded that these measures have acceptable reliability and validity.[2] Macleod et al suggest that the association between early cannabis use and subsequent drug use may have arisen from uncontrolled sources of confounding. As we acknowledged in our article, this remains a possibility. While they do not speculate on possible sources of uncontrolled confounding, it has often been suggested that such factors are likely to involve either aspects of the familial environment or heritable influences. Our study was designed as a test of this hypothesis and, to our surprise, we found that familial factors do not explain the association.

Macleod et al question the concept of "gateway effects." In fact, gateway effects have long been suspected as among the possible harms of cannabis; our analyses, consistent with the logic of scientific enquiry, were an attempt to falsify this hypothesis. We do not claim that we have proved the gateway hypothesis but, given previous arguments about potential sources of confounding and the novelty of our approach, we believe that our results are remarkable in that they failed to disprove this hypothesis. Nonetheless, further research is needed to rigorously test the gateway hypothesis. Given the known heritable influences on drug use[3,4] and the substantially reduced associations we report relative to previous studies, we believe that the most rigorous tests of this hypothesis will occur within the context of genetically informative research designs.[5] One promising but underused research strategy involves a children-of-twins design that allows both control for potentially confounding genetic risks and examination of gene-environment interactions.

Finally, we doubt that the association between early drug exposure and later cannabis use would be confounded by obstetric drug administration, as Dr Anand suggests. We agree that twins would be equally exposed to such drugs and thus, our use of a co-twin control design provides effective control for such exposures.

Michael T. Lynskey, PhD
Dixie J. Statham, MA
Nicholas G. Martin, PhD
Queensland Institute of Medical Research
Brisbane, Australia
Andrew C. Heath, DPhil
Kathleen K. Bucholz, PhD
Pamela A. F. Madden, PhD
Elliot C. Nelson, MD
Missouri Alcoholism Research Center
and Department of Psychiatry
Washington University School of Medicine
St Louis

Wendy S. Slutske, PhD
Missouri Alcoholism Research Center
and Department of Psychology
University of Missouri, Columbia

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In Reply: Dr Anand raises 2 issues in epidemiological research on the etiology of substance abuse.

First, he suggests that the models tested by Lynskey et al[1] were misspecified. Assuming that administration of opiates or other drugs to mothers at the time of delivery does increase the risk of drug addiction in offspring, does the omission of this factor in the analysis of Lynskey et al affect their conclusions in any way? I agree with Anand that the conclusions of Lynskey et al are not invalidated by the lack of attention to perinatal exposure to obstetric pain medication at the time of delivery. Both twins were similarly exposed to the putative perinatal causal factor. In a twin design, perinatal experiences are part of the shared influences that are held constant for subjects.

The second issue is how important a risk factor for drug addiction in offspring is giving drugs to mothers at the time of delivery. The evidence cited by Anand consists of the data from 3 case-control studies.[2-4] In the absence of further replications and of data from representative population samples, it is difficult to evaluate the effect of obstetric pain medication administered to a mother on subsequent substance use or abuse by offspring compared with that of other risk factors. Furthermore, exposure to opiates at the time of delivery may be a less important pregnancy-related risk factor than prolonged in utero exposure to maternal consumption of legal and illegal drugs in pregnancy. For instance, in utero exposure to maternal smoking has been linked to increased risk of offspring smoking in adolescence[5] and of substance abuse disorders in early adulthood.[6]

Moreover, my goal was not to identify all the potential determinants of the use or abuse of illicit substances other than marijuana, but rather to consider the strengths and weaknesses of various strategies for determining whether marijuana use has a truly causal role in the progression to the use of other illicit drugs.

Denise B. Kandel, PhD
Columbia University and
New York State Psychiatric Institute
New York

1. Lynskey MT, Heath AC, Bucholz KK, et al. Escalation of drug use in early-onset cannabis users vs co-twin controls. *JAMA.* 2003;289:427-433.