ORIGINAL CONTRIBUTIONS

Cannabis Use and Psychosis: A Longitudinal Population-based Study

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Cannabis use may increase the risk of psychotic disorders and result in a poor prognosis for those with an established vulnerability to psychosis. A 3-year follow-up (1997–1999) is reported of a general population of 4,045 psychosis-free persons and of 59 subjects in the Netherlands with a baseline diagnosis of psychotic disorder. Substance use was assessed at baseline, 1-year follow-up, and 3-year follow-up. Baseline cannabis use predicted the presence at follow-up of any level of psychotic symptoms (adjusted odds ratio (OR) = 2.76, 95% confidence interval (CI): 1.18, 6.47), as well as a severe level of psychotic symptoms (OR = 24.17, 95% CI: 5.44, 107.46), and clinician assessment of the need for care for psychotic symptoms (OR = 12.01, 95% CI: 2.24, 64.34). The effect of baseline cannabis use was stronger than the effect at 1-year and 3-year follow-up, and more than 50% of the psychosis diagnoses could be attributed to cannabis use. On the additive scale, the effect of cannabis use was much stronger in those with a baseline diagnosis of psychotic disorder (risk difference, 54.7%) than in those without (risk difference, 2.2%; p for interaction = 0.001). Results confirm previous suggestions that cannabis use increases the risk of both the incidence of psychosis in psychosis-free persons and a poor prognosis for those with an established vulnerability to psychotic disorder. *Am J Epidemiol* 2002;156:319–27.

cannabis; drug utilization; psychoses, substance-induced; psychotic disorders; schizophrenia

Abbreviations: BPRS, Brief Psychiatric Rating Scale; CI, confidence interval; CIDI, Composite International Diagnostic Interview; DSM-III-R, *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised; OR, odds ratio; T1, time 1 (between baseline and 1997); T2, time 2 (between 1997 (T1) and 1999).

Although converging epidemiologic findings demonstrate that the prevalence of cannabis use is higher among subjects with psychosis than among subjects from the general population (1–3), the mechanisms underlying this comorbid association have not been identified fully (4, 5). It is unclear whether subjects with incipient psychosis use cannabis to self-medicate their psychotic symptoms or, conversely, whether exposure to cannabis is a risk factor for onset of psychosis (6, 7). Because this issue cannot be disentangled by using cross-sectional or retrospective studies, prospective studies are essential to examine the temporal relation between cannabis use and emergence of psychosis.

A previous Swedish study (8) showed that young men using large quantities of cannabis at conscription were at increased risk of being admitted for schizophrenia over the subsequent 15-year period. However, to our knowledge, these findings have not yet been replicated in another population-based sample. Furthermore, the Swedish study was hampered by several limitations, such as the lack of information on drug use over the follow-up period and the fact that

psychosis cases were restricted to persons requiring hospital admission.

Another unsolved question regarding the link between cannabis use and psychosis is whether the impact of cannabis use on subsequent psychosis, if any, is stronger in subjects with a preexisting vulnerability to psychosis (9, 10). Several studies of subjects with a hospital diagnosis of psychosis have found that cannabis users have a poorer prognosis than nonusers do (6, 11–13). Since these findings were obtained in clinical samples, several factors linked to hospital-based recruitment of subjects may confound the association between cannabis use and poor outcome in subjects with an established vulnerability to psychosis.

The aims of the present study were to test the following hypotheses in a population-based sample of subjects followed up over 3 years. First, cannabis use increases the risk of psychosis, independent of the use of other drugs; second, those with an established vulnerability to psychotic disorder are more susceptible to this risk-increasing effect.

MATERIALS AND METHODS

Sample

This study was part of the Netherlands Mental Health Survey and Incidence Study (NEMESIS), a longitudinal study of the prevalence, incidence, course, and consequences of psychiatric disorders in the Dutch general population. The local ethics committee approved the study proposal as well as the manner in which informed consent was obtained from subjects. Subjects were contacted three times: in 1996 (baseline), in 1997 (T1—assessing the period between baseline and T1), and in 1999 (T2—assessing the period between T1 and T2) (14, 15).

A multistage, stratified, random sampling procedure was used to identify the sample. First, 90 municipalities were sampled randomly. Second, addresses of private households were selected randomly. Third, the person in the private household who had had the most recent birthday and was aged 18–64 years was asked to participate. Persons living in institutions, including those residing in psychiatric hospitals, were not included in the sampling frame. A total of 7,076 subjects were enlisted at baseline. The response rate was 69.7 percent. No difference in psychiatric morbidity based on the 12-item General Health Questionnaire was found between responders and nonresponders (14, 15). At T1, 5,618 subjects participated for the second time; at T2, 4,848 subjects participated.

Instruments

The study sample was interviewed at home by using the Composite International Diagnostic Interview (CIDI), version 1.1 (16) for all three measurements. The CIDI generates *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised (DSM-III-R) diagnoses and is designed for trained interviewers who are not clinicians. Interviewers read the questions and record respondents' answers, making the CIDI essentially a self-report instrument (17). The CIDI psychosis section (G) consists of 17 core psychosis items (G1–G13, G15, G16, G20, and G21) on delusions (13 items) and hallucinations (four items). These psychosis items correspond to classic psychotic symptoms such as persecution, thought interference, auditory hallucinations, and passivity phenomena.

Clinical reinterviews for psychotic symptoms

Because psychotic symptoms may be difficult to diagnose by lay interviewers, especially the clinical relevance of such symptoms (18–20), clinical reinterviews were conducted by telephone by an experienced clinician (psychiatrist, senior psychiatric trainee, or psychologist) for all subjects who had evidence of significant psychosis at baseline and at T2 (21, 22). Since the yearly incidence of psychosis is very low, no attempt was made to conduct clinical reinterviews at T1, just 1 year after the baseline interview. However, cases of psychosis that were incident between baseline and T1 would still have been identified at the T2 interview if the subjects continued to experience symptoms between T1 and T2, which is likely for the majority of cases who had any significant level of psychotic symptoms. The proportions of eligible subjects who were reinterviewed successfully by the clinician were 47.2 percent at baseline and 74.4 percent at T2.

The reinterviews were conducted by using questions from the Structured Clinical Interview for DSM-III-R (SCID), an instrument with proven reliability and validity in diagnosing schizophrenia (21). If the clinician's CIDI psychosis symptom rating did not coincide with that of the lay interviewer, the rating of the lay interviewer was replaced with that of the clinician. These corrected CIDI ratings were then entered into the CIDI diagnostic program. The DSM-III-R diagnoses of psychotic disorder at baseline were thus based on the Structured Clinical Interview for DSM-III-R data from these clinical reinterviews. Since no assessment of the need for treatment was made at baseline for subjects with a DSM-III-R diagnosis of psychosis (see below), this group included subjects who were clinical psychosis cases but also subjects whose psychotic experiences were not associated with the need for treatment. Thus, these subjects are hereafter referred to in this paper as persons with an established vulnerability to psychosis.

T2 assessment of incident psychotic symptoms

At T2, three Brief Psychiatric Rating Scale (BPRS) items (22)—"unusual thought content," "hallucinations," and "conceptual disorganization"—were additionally scored by the clinician who conducted the telephone clinical reinterview. The scores for each symptom ranged from 1, "absent" to 7, "very severe." Ratings of 2–3 indicate nonpathologic intensities of symptoms, and 4–7 indicate pathologic intensities of symptoms (23). The BPRS items "unusual thought content" and "hallucinations" represent the positive symptoms for psychosis and were used in the analyses in two ways: 1) any rating of more than 1 for either of these items (hereafter referred to as BPRS any psychosis) and 2) any rating of 4 or more on either of these items (hereafter referred to as BPRS pathology-level psychosis). To skew the

sample toward subjects with a lifetime first-ever occurrence of symptoms, we included only those subjects who, at the baseline interview, had a rating of lifetime *absence* for all of the individual items in the CIDI psychosis section.

T2 assessment of incident cases of psychosis

Since the most widely used system of classifying psychiatric disorders, the DSM-III-R (24), allocates "patient status" on the basis of disability and distress rather than clinical need, and persons in need of treatment may not be identified reliably, especially in population-based research (25), we used a procedure yielding a needs-based diagnosis to identify incident cases of psychosis at T2. Following each interview by clinicians at T2, a consensus meeting was organized that was attended by two psychologists and two psychiatrists, during which all available information regarding the case of psychosis was presented by the person who had conducted the telephone interview. The four clinicians reached a consensus regarding whether there was a need for mental health care in the context of psychotic symptoms, as defined in the Camberwell Assessment of Need (CAN) (26). The diagnoses that resulted from the consensus meeting were categorized as 1) no need for care in relation to psychotic symptoms or 2) probable or definite need for care in relation to psychotic symptoms. Validation of the needs-based diagnosis has been described in previous papers (M. Hanssen, Maastricht University, unpublished manuscript; M. Bak, Maastricht University, unpublished manuscript).

Drug use assessment

The L section of CIDI assesses use of a variety of substances. Included in the current analyses were questions about the following substances: cannabis, psychostimulants, cocaine, phencyclidine (PCP), and psychedelics. Psychostimulants, cocaine, phencyclidine, and psychedelics were combined into one group of "other drugs." Two types of exposure variables were constructed: 1) any use (hereafter referred to as any use) and 2) frequency of use over all three assessment periods (hereafter referred to as cumulative frequency). Any use at baseline, T1, or T2 was defined as any frequency of use (lifetime any use at baseline, use over the previous period at T1 and T2). Frequency of use during the period of heaviest use was expressed on a 1–5 scale (nearly every day, 3–4 days per week, 1–2 days per week, 1–3 days per month, less than once a month). Cumulative frequency was the overall longitudinal exposure defined as the sum of the five-level frequency ratings at baseline, T1, and T2. This score, with a range of 1–15, was also divided into three groups (1–5, 6–10, 11–15).

Analyses

Associations between cannabis use and psychosis outcome. Associations between drug use and psychosis outcome were expressed as odds ratios. The odds ratio expressed the risk of developing the psychosis outcome for those using drugs relative to those not using drugs. Adjusted odds ratios were computed by using logistic regression (27)

in the STATA statistical software program (28). All analyses were a priori adjusted for age (10-year groups), sex, ethnic group (0, subject and both parents born in the Netherlands; 1, other), level of education (four levels), unemployment, and single marital status. In addition, we also controlled for two previous risk factors for psychosis identified in the cohort: urbanicity (three levels) and experience with discrimination (four levels) (29).

To examine whether the effect of cannabis use at baseline on psychosis at follow-up was a proxy effect of cannabis use at follow-up, we entered cannabis any use at baseline, cannabis any use at T1 follow-up, and cannabis any use at T2 follow-up simultaneously in the adjusted models of the two psychosis outcomes. To assess whether any effect of cannabis was independent of use of other drugs associated with psychosis, models in which cannabis and other drugs were entered jointly were compared with models in which cannabis and other drugs were entered separately.

Risk set and sensitivity analyses. All of the analyses, with the exception of the interaction effects (see below), were conducted in the group of subjects who 1) at baseline, had a score of lifetime absence for all individual items in the CIDI psychosis section (5,838 of 7,076 subjects, 82.5 percent (30)); 2) had had a CIDI interview at T2 (n = 4,848); and 3) at T2, had not missed being reinterviewed by clinicians about the presence of psychotic symptoms if they had been eligible for this clinical reinterview. This risk set included 4,045 subjects. To check for possible fluctuations in sample demographic stability occasioned by conditions 1 and 2, the age and sex distributions of the groups identified by conditions 1 and 2 were compared with the risk set of 4,045 subjects. The proportion of men across the groups of 5,838 (condition 1), 4,848 (condition 2), and 4,045 (risk set) was 52.6, 53.5, and 52.7 percent, respectively, and mean age was 41.6, 41.2, and 41.5 years, respectively.

Because we did not reinterview all of the eligible subjects at T2 who had shown evidence of psychosis (the clinical reinterview rate at T2 was 74.4 percent, as noted above), we conducted sensitivity analyses to examine whether differential attrition could have biased any findings. These analyses were performed by substituting missing data, for the subjects who had missed clinical reinterview, in such a way that the extremes of any bias could be quantified. In the first sensitivity analysis, all missing subjects were allocated to the category of caseness of BPRS pathology-level psychosis; in the second type of analysis, all missing subjects were allocated to the category of noncaseness. In the same manner, we tested whether attrition in the sample as a whole (n = 7,076 at baseline, n = 4,848 at T2) could have biased the findings.

Population attributable fraction. The population attributable risk fraction, or the proportion of psychosis outcomes that could have been prevented if cannabis use 1) were a causal risk factor and 2) were eliminated completely from the population, is a measure of the public health importance of an exposure. It was derived from the adjusted associations between cannabis use and psychosis in the logistic regression models by using the AFLOGIT procedure in STATA software (28), which allows for estimating the population attributable fraction from within a logistic regression framework, thus enabling confounders to be taken into account.

TABLE 1. Patterns of cannabis use and psychosis outcome, the Netherlands Mental Health Survey and Incidence Study, 1996–1999

Cannabis exposure	T2* psychosis outcome											
	BPRS* any psychosis				BPRS pathology-level psychosis				Needs-based diagnosis of psychotic disorder			
	Outcome–* (n = 4,007)		Outcome+* (n = 38)		Outcome– (n = 4,035)		Outcome+ (n = 10)		Outcome– (n = 4,038)		Outcome+ (n = 7)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Baseline any use	304	7.59	8	21.05	305	7.56	7	70	308	7.63	4	57.14
Cumulative frequency†												
No use	3,622	91.7	30	79.0	3,649	91.7	3	30.0	3,649	91.6	3	42.9
Lowest level	264	6.7	3	7.9	265	6.7	2	20.0	265	6.7	2	28.6
Middle level	34	0.9	2	5.3	34	0.9	2	20.0	36	0.9	0	
Highest level	32	0.8	3	7.9	32	0.8	3	30.0	33	0.8	2	28.6

* T2, time 2 (between 1997 and 1999); BPRS, Brief Psychiatric Rating Scale (Psychol Rep 1962;10:799–812); –, absence of the outcome; +, presence of the outcome.
† Some percentages do not total 100 because of rounding.

Interaction between cannabis use and vulnerability to psychosis. To assess the effect of cannabis in those with an established vulnerability to psychosis, the effect of cannabis on the psychosis outcomes at T2 was estimated in the group of subjects who, at baseline, had had a DSM-III-R lifetime diagnosis of any affective or nonaffective psychotic disorder (n = 59 with baseline and T2 outcome data) and was then compared with the effect of cannabis in the risk set (n = 4,045). The group of 59 subjects who had a psychotic disorder and T2 outcome data came from a larger group of 107 who had a baseline DSM-III-R diagnosis of psychotic disorder. A comparison between the 59 psychosis cases with and the 48 without T2 outcome data revealed no differences in terms of baseline cannabis use ($\chi^2 = 1.0$, df = 1, $p = 0.31$), age ($t = -0.55$, df = 105, $p = 0.58$), or sex ($\chi^2 = 2.7$, df = 1, $p = 0.10$). In line with recent advances in the conceptualization of interaction, we calculated the statistical additive interaction and estimated from that the population amount of biologic synergism between cannabis use and psychosis vulnerability (refer to the Appendix) (31). To calculate the statistical interaction under an additive model, the BINREG procedure in STATA software (28), which fits generalized linear models for the binomial family estimating risk differences, was used to model interactions between cannabis (any use) and psychosis vulnerability (any lifetime diagnosis of psychosis).

RESULTS

Cannabis use and psychosis

In the risk set of 4,045 subjects who, at the baseline interview, had a rating of lifetime absence for all individual items in the CIDI psychosis section, seven subjects (0.17 percent) at T2 had a probable/definite need for care related to psychotic symptoms. The number of subjects at T2 with BPRS any psychosis was 38 (0.94 percent), and the number with BPRS pathology-level psychosis was 10 (0.25 percent).

Subjects with a psychosis outcome at T2 had higher levels of cannabis use at baseline (table 1). Cannabis any use at baseline and cumulative frequency were associated with a high risk of psychosis outcome at T2 (table 2). The associations generally remained significant after adjustment for age, sex, ethnic group, single marital status, level of education, urbanicity, and level of discrimination. Additional adjustment for the presence of any CIDI lifetime diagnosis at baseline (to exclude the possibility that cannabis use at baseline was secondary to a nonpsychotic DSM-III-R diagnosis, which, in turn, was a prodrome of later psychosis) changed the parameters by only a tiny amount (e.g., BPRS pathology-level outcome—cannabis any use at baseline: odds ratio (OR) = 23.32, 95 percent confidence interval (CI): 4.92, 110.50; cumulative frequency: OR = 4.17, 95 percent CI: 2.34, 7.42).

Distal versus proximal effects

For the three psychosis outcomes, the effect of baseline cannabis use was much stronger than the effects of more proximal cannabis use at T1 and T2. This finding indicated that the effects of cannabis use at baseline on psychosis at follow-up was not a proxy effect of cannabis use at follow-up (table 3).

Cannabis and other substances

Use of other drugs, as defined in Materials and Methods, was strongly associated with the three psychosis outcomes when entered separately in the model. However, when entered jointly with cannabis, the effects were greatly reduced or even disappeared altogether, while the effect of cannabis remained (table 4).

Population attributable fraction

The population attributable fraction was calculated for the "any use" exposure and the three outcomes. The population attributable fractions were 13.4 percent for BPRS any psychosis, 67.1 percent for BPRS pathology-level psychosis, and 50.4 percent for needs-based diagnosis of psychotic

TABLE 2.   Associations between cannabis use and time 2 psychosis outcome, the Netherlands Mental Health Survey and Incidence Study, 1996–1999

Cannabis exposure	T2* psychosis outcome											
	BPRS* any psychosis (n = 38)				BPRS pathology-level psychosis (n = 10)				Needs-based diagnosis of psychotic disorder (n = 7)			
	OR*	95% CI*	Adjusted† OR	95% CI	OR	95% CI	Adjusted† OR	95% CI	OR	95% CI	Adjusted† OR	95% CI
Baseline any use	3.25	1.48, 7.15	2.76	1.18, 6.47	28.54	7.34, 110.91	24.17	5.44, 107.46	16.15	3.60, 72.47	12.01	2.24, 64.34
Cumulative frequency												
No use‡	1		1		1		1		1		1	
Lowest level	1.37	0.42, 4.52	1.23	0.36, 4.23	9.18	1.53, 55.18	7.90	1.15, 54.09	9.18	1.53, 55.18	5.10	0.66, 39.21
Middle level	7.10	1.63, 30.91	4.90	10.4, 23.14	71.55	11.58, 441.94	54.46	7.17, 413.73	—§		—§	
Highest level	11.32	3.29, 38.99	6.81	1.79, 25.92	114.03	22.17, 586.50	74.67	11.76, 474.32	73.72	11.92, 455.76	47.77	5.91, 385.94
Linear trend¶	2.23	1.53, 3.24	1.89	1.25, 2.85	4.96	3.08, 8.00	4.27	2.44, 7.45	3.97	2.22, 7.10	3.53	1.76, 7.09

* T2, time 2 (between 1997 and 1999); BPRS, Brief Psychiatric Rating Scale (Psychol Rep 1962;10:799–812); OR, odds ratio; CI, confidence interval.

† Adjusted for age, sex, ethnic group, single marital status, level of education, urbanicity, and level of discrimination.

‡ Reference category.

§ No exposed persons had the outcome.

¶ The increase in risk with one unit change in cannabis frequency.

disorder. These fractions indicated that, assuming that the relation between cannabis use and psychosis is causal, the incidence of the three psychosis outcomes would be reduced by 13, 67, and 50 percent, respectively, if the cannabis exposure were eliminated from the population.

Interaction with vulnerability to psychosis

Of the 59 subjects with a DSM-III-R diagnosis of any psychosis at baseline for whom follow-up data at T2 were available, nine (15.3 percent) reported cannabis any use at

baseline. In the risk set, this proportion was 7.7 percent (n = 312). On the additive scale, the increase in the risk of having the psychosis outcome at T2 was much higher in the group with a baseline diagnosis of psychotic disorder than in that without such a diagnosis, although the increase was still significant in the latter group. The difference in risk between those with and without psychotic disorder at baseline was statistically significant for two psychosis outcomes (table 5). By following the procedure developed by Darroch (31) (refer to the Appendix), we calculated what proportion of the BPRS pathology-level psychosis outcome in subjects both

TABLE 3.   Effects of cannabis use distal and proximal to psychosis outcome, the Netherlands Mental Health Survey and Incidence Study, 1996–1999

Drug exposure	T2* psychosis outcome					
	BPRS* any psychosis (n = 38)		BPRS pathology-level psychosis (n = 10)		Needs-based diagnosis of psychotic disorder (n = 7)	
	Adjusted† OR*	95% CI*	Adjusted† OR	95% CI	Adjusted† OR	95% CI
Separate effects						
Any use at baseline	2.76	1.18, 6.47	24.17	5.44, 107.46	12.01	2.24, 64.34
Any use at T1*	2.96	0.96, 9.22	14.91	3.39, 65.57	11.07	1.62, 75.76
Any use at T2	3.17	1.02, 9.92	15.08	3.35, 68.00	9.36	1.39, 63.13
Jointly entered in the same model						
Any use at baseline	2.22	0.78, 6.31	15.78	2.83, 88.05	7.73	1.09, 54.74
Any use at T1	1.13	0.18, 7.15	1.35	0.14, 13.11	1.75	0.08, 40.35
Any use at T2	1.68	0.28, 10.19	2.32	0.25, 21.90	1.86	0.09, 38.52

* T2, time 2 (between 1997 (T1) and 1999); BPRS, Brief Psychiatric Rating Scale (Psychol Rep 1962;10:799–812); OR, odds ratio; CI, confidence interval; T1, time 1 (between baseline and 1997).

† Adjusted for age, sex, ethnic group, single marital status, level of education, urbanicity, and level of discrimination; reference category, those subjects who did not use cannabis at the three specified time points.

TABLE 4. Effects of cannabis use on psychosis in relation to use of other substances, the Netherlands Mental Health Survey and Incidence Study, 1996–1999

Drug exposure	T2* psychosis outcome					
	BPRS* any psychosis (n = 38)		BPRS pathology-level psychosis (n = 10)		Needs-based diagnosis of psychotic disorder (n = 7)	
	Adjusted† OR*	95% CI*	Adjusted† OR	95% CI	Adjusted† OR	95% CI
Separate effects						
Baseline any use						
Cannabis‡	2.76	1.18, 6.47	24.17	5.44, 107.46	12.01	2.24, 64.34
Other drugs‡,§	5.38	1.48, 19.56	23.47	4.99, 110.35	9.55	0.90, 101.52
Cumulative frequency¶						
Cannabis‡	1.89	1.25, 2.85	4.27	2.44, 7.45	3.53	1.76, 7.09
Other drugs‡	2.57	1.31, 5.04	4.59	2.17, 9.74	2.84	0.95, 8.49
Jointly entered in the same model						
Baseline any use						
Cannabis‡	2.11	0.78, 5.71	16.93	3.33, 86.13	10.51	1.75, 63.21
Other drugs‡	2.99	0.68, 13.25	3.95	0.77, 20.27	1.89	0.15, 23.57
Cumulative frequency¶						
Cannabis‡	1.65	1.00, 2.73	3.73	1.99, 7.01	3.47	1.64, 7.37
Other drugs‡	1.64	0.71, 3.80	1.83	0.75, 4.50	1.09	0.26, 4.52

* T2, time 2 (between 1997 and 1999); BPRS, Brief Psychiatric Rating Scale (Psychol Rep 1962;10:799–812); OR, odds ratio; CI, confidence interval.

† Adjusted for age, sex, ethnic group, single marital status, level of education, urbanicity, and level of discrimination.

‡ Reference category, those subjects who did not use cannabis or other drugs at baseline (baseline any use) or at all three time points (cumulative frequency).

§ Psychostimulants, cocaine, phencyclidine (PCP), and psychedelics were combined into one group of "other drugs."

¶ Linear trend for the adjusted odds ratio: an increase in risk with one unit change in cannabis frequency.

exposed to cannabis and having an established vulnerability to psychosis was attributable to the synergistic action of these two factors. This calculation revealed that between 79 and 82 percent was due to the synergistic action of these two factors.

Sensitivity analyses

The results regarding the BPRS pathology-level psychosis outcome and missing clinical reinterview data were as follows: 1) assuming that all subjects for whom values were missing were noncases—cannabis any use: OR = 24.36, 95 percent CI: 5.48, 108.37; cannabis cumulative frequency: OR = 4.27, 95 percent CI: 2.45, 7.47; and 2) assuming that all subjects for whom values were missing were cases—cannabis any use: OR = 3.30, 95 percent CI: 1.30, 8.33; cannabis cumulative frequency: OR = 2.17, 95 percent CI: 1.41, 3.34. The results regarding the BPRS pathology-level psychosis outcome and missing data due to general sample attrition were as follows: 1) assuming that all subjects for whom values

TABLE 5. Interactions between cannabis any use and existing vulnerability to psychosis on the additive scale (risk difference), the Netherlands Mental Health Survey and Incidence Study, 1996–1999

	BPRS* any psychosis (n = 54)		BPRS pathology-level psychosis (n = 22)		Needs-based diagnosis of psychotic disorder (n = 15)	
	Increase (%)	95% CI*	Increase (%)	95% CI	Increase (%)	95% CI
Increase in risk† associated with baseline cannabis any use						
No psychosis (n = 4,045)	1.8	0.0, 3.5	2.2	0.5, 3.8	1.3	−0.05, 2.5
Any psychosis (n = 59)	46.7	13.9, 79.4	54.7	22.6, 86.8	23.3	−8.6, 55.2
Additive interaction‡	$\chi^2 = 7.21$, df = 1, $p = 0.0073$		$\chi^2 = 10.26$, df = 1, $p = 0.0014$		$\chi^2 = 1.85$, df = 1, $p = 0.17$	

* BPRS, Brief Psychiatric Rating Scale (Psychol Rep 1962;10:799–812); CI, confidence interval.

† Risk of having the psychosis outcome at T2 (time 2 (between 1997 and 1999)).

‡ Tests whether an increase in risk in the "any psychosis" group is significantly greater than an increase in risk in the "no psychosis" group.

were missing were noncases—cannabis any use: OR = 25.17, 95 percent CI: 5.64, 112.24; cannabis cumulative frequency: OR = 4.27, 95 percent CI: 2.44, 7.45; and 2) assuming that all subjects for whom values were missing were cases—cannabis any use: OR = 1.11, 95 percent CI: 0.89, 1.38; cannabis cumulative frequency: OR = 4.27, 95 percent CI: 2.44, 7.45.

DISCUSSION

This population-based prospective study showed that a baseline history of cannabis use increased the risk of a follow-up psychosis outcome for subjects with a lifetime absence of psychosis, with a dose-response relation between exposure load and psychosis outcome. A baseline lifetime history of cannabis use was a stronger predictor of psychosis outcome than was use over the follow-up period and use of other drugs. A strong additive interaction was found between cannabis use and established vulnerability to psychotic disorder: the difference in risk of psychosis at follow-up between those who did and did not use cannabis was much stronger for those with an established vulnerability to psychosis at baseline than for those without one. Sensitivity analyses showed that differential attrition was unlikely to have contributed to the results. In addition, previous analyses of this sample have shown that psychopathology had only weak-to-moderate effects on attrition at T1 (32).

The present findings have to be interpreted in light of potential methodological limitations. We cannot exclude underreporting of drug use, because it was assessed by using self-reported data and was not confirmed with toxicologic screening. However, urine testing does not provide information on lifetime use, and there is little reason to suspect that cannabis use was underreported; personal use of cannabis is legal in the Netherlands, and cannabis is widely accepted as a recreational drug. As a consequence of the limited number of subjects who had a needs-based psychotic disorder, the effect size of some associations could not be calculated, and some interval estimations were imprecise. Some cases of psychosis arising between baseline and T1, when no clinical reinterviews were conducted, may have been missed at the T2 interview if subjects' symptoms did not persist beyond the T1 interview. This possibility could, in theory, have biased our findings if these had been the cases in which cannabis had no effect, or a protective effect, on the development of psychotic symptoms. However, when we examined the association between baseline any cannabis use and any self-report of psychotic symptoms at T1 in subjects who had been psychosis free at baseline, the odds ratio was large and in the same direction (OR = 2.64, 95 percent CI: 1.54, 4.52). Although this association was based on self-reported psychotic symptoms at T1 instead of clinical assessment, it is unlikely that clinical reinterview would have substantially changed the strength or direction of this association.

In accordance with the findings reported by Andreasson et al. (8), the present study shows that psychosis-free subjects who have a lifetime history of cannabis use are at increased risk of a psychosis outcome. As in the Swedish study (8), further evidence supporting the hypothesis of a causal relation is demonstrated by the existence of a dose-response

relation (33) between cumulative exposure to cannabis use and the psychosis outcome.

The strengths of the present study are that drug use was documented in the context of a structured diagnostic interview at baseline and over the follow-up period and that definition of psychosis outcome was not restricted to cases of psychosis requiring hospitalization, which are but the extreme of a continuum of psychotic experiences (29). Thus, the present findings provide answers to questions raised by the Swedish cohort study (8). First, the association between cannabis use and psychosis outcome is not restricted to the most severe outcome; that is, there is a continuum of risk ranging from increased occurrence of psychotic symptoms to incidence of cases in need of treatment. Second, the association is independent of use of other drugs at baseline and over the follow-up period. Third, the finding that psychosis outcome is more strongly predicted by a baseline lifetime history of use than by recent use contributes to clarifying the temporal relation between cannabis exposure and increased risk of psychosis. This finding suggests that this association is not fully explained by the short-term effects of cannabis leading to acute occurrence of psychotic experiences (5).

Any claim of a causal relation between cannabis use and psychosis would be further supported by a plausible biologic mechanism (33, 34). Long-term effects of cannabis on the risk of psychosis outcome may be due to long-lasting dysregulation of endogenous anadamide/cannabinoid systems mediating the effects of tetrahydrocannabinol on the brain. Other neurotransmission systems modulated by cannabinoid receptors may also be involved. Some recent findings indirectly support this cannabinoid-receptor hypothesis. An increased density of cannabinoid-1 receptors has been found in the caudate-putamen of cannabis users (35), and there are close interactions between cannabinoid and dopaminergic systems (36) that are thought to underlie psychotic symptoms. Experimental evidence in rodents has demonstrated that chronic exposure to delta9-tetrahydrocannabinol induces sensitization of monoaminergic neurotransmitter systems thought to be involved in psychosis (37). A limited number of studies have reported changes in the endogenous cannabinoid concentration (38) or in the number of cannabinoid receptors (35) in subjects who have schizophrenia. These findings, which have to be interpreted with caution since they have been obtained in samples of patients with chronic disease, nevertheless suggest that dysregulation of the cannabinoid system may be implicated in the pathophysiology of psychosis. It can be hypothesized that the neurobiologic changes induced by tetrahydrocannabinol may interact with a preexisting vulnerability to dysregulation of the cannabinoid system or to other neurotransmission systems interacting with the cannabinoid system. In accordance with this hypothesis, the present findings demonstrate that the impact of cannabis use on psychosis outcome is especially marked in subjects with an established vulnerability to psychosis. The difference in the risk of psychosis at follow-up between those who did and did not use cannabis was much stronger for those with a baseline vulnerability to psychosis (54.7 percent) than for those without a baseline experience of psychosis (2.2 percent).

About 80 percent of the psychosis outcome associated with exposure to both cannabis and an established vulnera-

bility to psychosis was attributable to the synergistic action of these two factors. This finding indicates that, of the subjects exposed to both a vulnerability to psychosis and cannabis use, approximately 80 percent had the psychosis outcome because of the combined action of the two risk factors and only about 20 percent because of the action of either factor alone.

In conclusion, this prospective study confirms previous suggestions that cannabis use is an independent risk factor for the emergence of psychosis in psychosis-free persons and that those with an established vulnerability to psychotic disorder are particularly sensitive to its effects, resulting in a poor outcome. These findings have public health implications. If a causal relation between cannabis use and psychosis outcome is assumed, the population attributable fraction—that is, the maximum proportion of psychosis outcomes attributable to cannabis use in psychosis-free subjects—is higher than 50 percent. Although this high percentage can be misleading because it also includes the effects of all other causal risk factors that interact with cannabis, there is nevertheless cause for concern given the widespread use of cannabis by adolescents and young adults (39–41). The percentage of cases that may be prevented by suppressing exposure to this risk factor may not be negligible.

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APPENDIX

Estimating the Amount of Biologic Synergism between Two Causes

Let us assume that there are two risk factors for schizophrenia, E and G. *Risk* is a measure of the proportion of persons who develop schizophrenia. If there are two risk factors, G and E, there are four possible exposure states according to whether each factor is present (+) or absent (−), and each of these four exposure states carries a specific risk. Thus, the risk of schizophrenia in the population exposed to E only is $R(E)$, and the risk in the population exposed to G only is $R(G)$. The risk of schizophrenia in the population exposed to neither E nor G is R, whereas the risk in the population exposed to both G and E is $R(GE)$. On the additive scale, the *effect* of a risk factor is expressed as a *risk difference*. For example, if $R(G)$ is 0.25 and R is 0.10, the effect of G is 0.25 − 0.10 = 0.15. We can thus express the effect of G as $R(G) − R$, the effect associated with E as $R(E) − R$, and the effect associated with the GE exposure as $R(GE) − R$. The following table shows the effects associated with the four different exposure states:

	$G-$	$G+$
$E-$	R	$R(G) - R$
$E+$	$R(E) - R$	$R(GE) - R$

Because the combined effect of G and E is $R(GE) − R$, the excess of this effect over the sum of the solitary effects of G and E is as follows: $[R(GE) − R] − [R(G) − R] − [R(E) − R] = [R(GE) − R(G) − R(E) + R]$.

If $[R(GE) − R(G) − R(E) + R] > 0$, G and E are said to interact on the additive scale. We will hereafter refer to $[R(GE) − R(G) − R(E) + R]$ as the statistical additive interaction.

How can we quantify the extent to which G and E act synergistically, that is, in some way depend on each other, or coparticipate, in disease causation? Let us consider the proportion of persons in the population who developed schizophrenia after exposure to both G and E, or $R(GE)$. It is possible that some of these persons would also have contracted the disorder after exposure to either G or E alone. The degree to which some persons would also have contracted the disorder after exposure to either G or E alone is referred to as the degree of *parallelism*. If there is parallelism, G and E "compete" to cause schizophrenia, and, the more they compete, the smaller the proportion of persons who contracted the disease because of the *coparticipation* of G and E. Thus, parallelism can be thought of as the opposite of synergism. For example, in the extreme case of 100 percent parallelism, where all persons exposed to G and E had developed the disease because of the causal action of either G or E alone, no person could have contracted schizophrenia because of the coparticipation of G and E. In this case, the amount of synergism would be zero. In practice, it is impossible to assess the amount of parallelism and the amount of synergy in persons exposed to both G and E. However, it can be shown that the amount by which synergism exceeds parallelism equals the excess of $R(GE)$ over the sum of the solitary effects of G and E (i.e., the statistical additive interaction as shown above) (33). In other words, |synergism| − |parallelism| = $[R(GE) − R(G) − R(E) + R]$.

The amount of synergy can then be approximated by using the following table (33):

|synergism| |$x1$|	|$x2$| |parallelism|	$R(GE) - R(G)$ $R(G) - R$
$R(GE) - R(E)$	$R(E) - R$	

The variables $x1$ and $x2$ are two unknowns that sum with synergism and parallelism to $[R(GE) − R(E)]$ and $[R(E) − R]$, respectively. In our study, the risks were $R = 0.08$ percent; $R(G) = 12$ percent, $R(E) = 2.2$ percent; and $R(GE) = 67$ percent. Filling in these risks in the table above reveals that synergism is 79–82 percent.