Schizophrenia Bulletin vol. 47 no. 3 pp. 594–603, 2021
doi:10.1093/schbul/sbab019
Advance Access publication 8 March 2021

Schizophrenia and the Environment: Within-Person Analyses May be Required to Yield Evidence of Unconfounded and Causal Association—The Example of Cannabis and Psychosis

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Hypotheses about the link between cannabis use and psychosis apply to the within-person level but have been tested mostly at the between-person level. We used a within-person design, in which a person serves as his own control, thus removing the need to consider confounding by any fixed (genetic and nongenetic) characteristic to study the prospective association between cannabis use and the incidence of attenuated psychotic experiences, and vice versa, adjusted for time-varying confounders. We combined 2 general population cohorts (at baseline: Early Developmental Stages of Psychopathology Study, *n* = 1395; Netherlands Mental Health Survey and Incidence Study-2, *n* = 6603), which applied a similar methodology to study cannabis use and attenuated psychotic experiences with repeated interviews (T0, T1, T2, and T3) over a period of approximately 10 years. The Hausman test was significant for the adjusted models, indicating the validity of the fixed-effects model. In the adjusted fixed-effects model, prior cannabis use was associated with psychotic experiences (aOR = 7.03, 95% CI: 2.39, 20.69), whereas prior psychotic experiences were not associated with cannabis use (aOR = 0.59, 95% CI: 0.21, 1.71). Longitudinal studies applying random-effects models to study associations between risk factors and mental health outcomes, as well as reverse causality, may not yield precise estimates. Cannabis likely impacts causally on psychosis but not the other way round.

Key words: cannabis/psychosis/within-person effects/epidemiology/drug use

Introduction

The pooled analysis of the association between cannabis and psychosis indicates approximately a 4-fold increase in risk for the heaviest users and a 2-fold increase for the average cannabis user in comparison to nonusers.[1,2] Observational studies on the association between cannabis use and psychosis outcomes commonly suffer from so-called omitted variable bias. This refers to the possibility that the observed link is due to any of a range of plausible confounders, beyond simple demographics and direct confounders, that can never be measured precisely in combination, such as genetic vulnerabilities, cognitive abilities, fetal exposures, early development, and parental rearing practices.

One way of comprehensively addressing omitted variable bias is to study within-person associations of cannabis and psychosis using panel data. Panel data (the same subjects measured at 2 or more points in time) consist of repeated measures that are nested within individuals. The repeated measures are referred to as the within-person level or level 1 units, whereas the persons are referred to

as the between-person level or level 2 units. Studies on the association between cannabis use and psychosis over time are usually analyzed at the between-person level or the mixed within-person and between-person level. However, the relationship between cannabis use and psychosis may well differ across levels (ie, between-person versus within-person levels). A classic example involves the relationship between physical exercise and heart rate: the within-person analysis will reveal a positive association in that more strenuous exercise leads to a higher heart rate. However, in contrast, this association is likely to be reversed at the between-person level, as people who exercise a lot, on average, tend to have a lower heart rate due to their overall better fitness.[3]

Panel data of individuals measured repeatedly over time allow control for fixed characteristics, including full nongenetic and genetic risk, whether they are measured/measurable or not, by analyzing, over time, associations with an exposure in the fixed-effect within-person model (FE) and contrasting these with the traditionally used random-effects model (RE) that combines within-person and between-person effects. The within-person effect compares psychosis outcomes in the same person across time when switching from *using* to *not using* cannabis and, therefore, cannot be confounded by stable characteristics, including nongenetic and genetic variation. To date, this has been examined in only very few studies. Fergusson et al studied 1055 young adults over time and found, using a within-person analysis, that cannabis use predicted psychotic symptoms and that the direction of causality was from cannabis use to psychotic symptoms rather than the other way round.[4] Bechtold et al, studying a sample of 1009 adolescent boys, repeatedly assessed over time and using a within-person analysis, found that cannabis use predicted subthreshold psychotic experiences but not the other way round.[5]

Although these 2 studies used relatively small samples, the results are consistent. The question arises, therefore, to what degree the results of within-person analyses may differ from traditional random-effects models that have shown more variable results, particularly with regard to the self-medication hypothesis.[6] Previous within-person analyses did not conduct such a comparison.[4,5] Also, a problem of fixed-effect exposure-outcome analysis is that it requires very large samples, as only individuals exhibiting a within-person change of exposure/outcome are informative. It is, therefore, important to further study longitudinal associations between cannabis use and psychosis, in both directions and in larger samples than available to date, at the within-person level, using panel data that allow for the use of participants as their own controls, and to compare the results with commonly used random-effects models.

With binary dependent variables, within-person analysis can be done with the use of conditional logit/fixed-effects logit models.[7] There are several prerequisites for using fixed-effects methods to study prospectively the association between cannabis use and psychosis: (1) the psychosis outcome must be measured on at least 2 occasions for each individual, one with and one without preceding cannabis use; (2) the cannabis exposure must change across time for a substantial portion of the individuals; (3) in the causal model (cannabis→psychosis), cannabis use must precede psychosis and, in the self-medication model (psychosis→cannabis), psychosis must precede cannabis use. In order to meet these 3 requirements together, panel data are required that consist of a baseline assessment and at least 3 follow-up assessments.

Attenuated psychotic states, the main component of "clinical high-risk" states, are the focus of much research focused on early intervention and prevention.[8–11] Here, we report (1) the unconfounded, longitudinal, within-person association between cannabis use and attenuated psychotic states, (2) the unconfounded, longitudinal within-person association between attenuated psychotic states and cannabis use (reverse causation), and (3) comparing the results with the traditional random-effects model for panel data, using 2 population cohorts with 4 interview waves and similar methodology, and together covering the entire relevant age range to assess attenuated psychosis outcomes, cannabis use, and possible time-varying confounders, thus evaluating the potential roles of the 3 explanations that can be brought to bear on the apparent association between cannabis use and psychosis.

Methods

Samples

The Early Developmental Stages of Psychopathology Study (EDSP) and Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2) are longitudinal cohort studies of the prevalence, incidence, course, and consequences of mental disorders in the Dutch (NEMESIS-2) and German (EDSP) general populations. Both had a baseline interview (T0) and 3 follow-up interviews (T1–T3), using a version of the Composite International Diagnostic Interview (CIDI),[12] and both are based on multistage, random sampling procedures of municipalities and households. Detailed information about the characteristics of these studies was published elsewhere.[13–16]

NEMESIS-2 was conducted to study the prevalence, incidence, course, and consequences of mental disorders in a random representative sample of the Dutch adult general population. The baseline data of NEMESIS-2 were collected from 2007 to 2009, follow-up was until 2018. Details of NEMESIS-2 are provided elsewhere.[13,17] The first wave (T0) enrolled 6,646 participants (response rate 65.1%; average interview duration: 95 min), who were followed up in 3 visits within 9 years: successive response rates at year 3 (T1), year 6 (T2), and year 9 (T3) were 80.4% (n = 5303;

excluding those who deceased; interview duration: 84 min), 87.8% (n = 4618; interview duration: 83 min), and 86.8% (n = 4007; interview duration: 102 min), respectively. Prevalence rates of mental disorders at baseline reflect lifetime occurrence; rates at T1–T3 reflect interval (baseline–T1, T1–T2, and T2–T3) occurrence of approximately 3 years. Attrition between T0 and T3 was not significantly associated with any of the mental disorders at T0, after controlling for sociodemographic characteristics.[18,19]

The EDSP is a prospective-longitudinal study in a German general population sample aged 14–24 years at baseline. The EDSP study collected information on the prevalence, incidence, risk factors, comorbidity, and course of mental symptoms and syndromes in a random representative community sample of 3021 adolescents and young adults living in the Munich area (aged 14–24 years at baseline) at 4 waves: at baseline (T0) and at 3 follow-ups after on average 1.6 (T1), 3.5 (T2), and 8.4 years (T3) after baseline, respectively. The first follow-up wave was conducted only in the subsample of respondents aged 14–17 years at T0, whereas the second and third follow-ups were again conducted for all respondents. Details are provided elsewhere.[14,15] As the requirement of 4 interview waves only applied to the respondents aged 14–17 years at baseline, only this subgroup of EDSP respondents (n = 1395; 46% of the sample at baseline) was included in the analyses.

In both studies, participants were interviewed using a version of the CIDI.[12] This is a comprehensive and standardized diagnostic interview assessing symptoms, syndromes, and diagnoses of mental disorders according to the diagnostic criteria of a version of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM). The instrument is designed for trained interviewers who are not clinicians. Questions are read in a standardized way and participants' answers are recorded by the interviewer. Therefore, the CIDI is essentially a self-report instrument.[20] Both the validity[21,22] and the test–retest reliability[23] have been established, showing that the CIDI provides valid diagnoses for almost all nonpsychotic disorders with good to excellent kappa coefficients for most diagnostic sections.

The EDSP project was approved by the Ethics Committee of the *Technische Universität Dresden*. NEMESIS-2 was conducted with the approval of the ethics committee of the Netherlands Institute of Mental Health and Addiction, Utrecht, the Netherlands. All respondents provided informed consent at each wave.

Psychotic Experiences

In NEMESIS-2, a psychosis add-on instrument based on the G section of the previous versions of the CIDI version 1.1 was included. This add-on instrument consists of 20 psychotic symptoms corresponding to the symptoms assessed in EDSP. In NEMESIS-2, an experienced clinician did a follow-up telephone interview with participants reporting a psychotic symptom to assess whether the self-report information about the psychotic symptom also qualified as psychotic according to the clinicians rating. In NEMESIS-2, a mean of 79% of all participants eligible for follow-up clinical interview at each of the 4 assessment waves was reassessed, and the CIDI rating was adjusted according to a clinical follow-up interview. Given similarities between CIDI self-reported and clinically validated psychotic experiences (PE), in terms of associations, predictive value, and outcome,[24–26] CIDI self-reported PE were preserved in the case clinical follow-up interview had not taken place, thus increasing statistical power. PE were dichotomized into "present" versus "absent," consistent with previous work in NEMESIS-2.[27,28]

In the EDSP, different assessments for PE were carried out at assessment waves T0 and T1 on the one hand, and at T2 and T3 on the other. At T2 and T3, PE were assessed using the G section of the M-CIDI, as described previously.[29,30] This section included 14 items about delusions and 5 items about hallucinations corresponding to classic psychotic symptoms like persecution, various hallucinations, and thought interference. The interviews were conducted by trained psychologists who were allowed to probe with follow-up clinical questions. At T0 and T1, as described previously,[31–33] a binary measure of PE was constructed using the psychoticism and paranoid ideation dimensions of the SCL-90-R, combining these 2 dimensions into a single "psychosis" dimension and using the 80th percentile cutoff to create a binary measure of PE. The 80th percentile cutoff was chosen to approximately match the prevalence of PE assessed with the CIDI at T2 and T3.

Cannabis Use

In NEMESIS-2, cannabis use was assessed in the section Illegal Substance Use of the CIDI 3.0. Conform previous work,[34] the cutoff of use of once per week or more in the period of most frequent use was used to define a binary variable for regular lifetime or interval cannabis use. In EDSP, cannabis use was assessed with the L-section of the DIA-X/M-CIDI using the question "Have you ever used cannabis five times or more?" to define cannabis exposure (lifetime use at baseline and interval use at follow-up interviews). Conforming to previous work,[32,35] the DIA-X/M-CIDI cutoff of use of 5 times or more was used to define the binary variable for cannabis exposure.

Other Drug Use

In both EDSP and NEMESIS-2, a binary variable was constructed at each time point to denote any lifetime or interval use (given very low rates of use) of drugs

associated with psychotic disorder: cocaine, stimulants, psychedelics/hallucinogens (mescaline, PCP, XTC, ketamine, LSD, and others).

Adulthood Stressful Life Events

In NEMESIS-2, based on the "Brugha Life events section",[36] participants were asked whether they experienced at least one of 9 life events within the last 12 months (T0) or since the last interview (T1 to T3). Examples of items are serious sickness, death of a family member or close friend, and serious financial problems. Conforming to our previous analyses in this cohort, life events were dichotomized into the present (≥1 life events) and absent (0 life events).[37] In EDSP, the Munich Interview for the Assessment of Life Events and Conditions (Münchner Ereignis Liste—MEL)[38] was used to assess baseline and interval occurrence of recent adversity. The MEL is a 3-step interview procedure for assessing recent adversity through recognition, rather than free recall, using a list of 84 very detailed and specific descriptions of positive and negative life events encompassing 11 dimensions.[38]

Any 12-Month DSM Diagnosis

In NEMESIS-2, the following CIDI, version 3.0, nonpsychotic DSM-IV diagnoses were assessed for the period of the last 12 months at each wave: major depression, dysthymia, bipolar disorder, any anxiety disorder, and any substance use disorder. In EDSP, any DSM-IV diagnosis was similarly defined as a 12-month diagnosis at each wave of any major depression, dysthymia, bipolar disorder, any anxiety disorder, and any substance use disorder.

Analyses

Risk Set Individuals with a diagnosis of psychotic disorder at baseline (Nemesis-2: $n = 43$, EDSP: $n = 0$) were excluded from the analysis. Individuals with a lifetime history of psychotic experiences at baseline were per definition excluded from the models testing the association between preceding cannabis use at timepoint t-1 and subsequent psychotic experiences at timepoint t, as the requirement was that individuals did not display evidence of psychosis at timepoint t.

Similarly, individuals at baseline with a lifetime history of cannabis use (and thus including the subgroup with cannabis use disorder) were per definition excluded from the models testing the association between preceding psychosis at timepoint t-1 and subsequent cannabis use at timepoint t, as the requirement was that individuals did not display evidence of cannabis use at timepoint t-1. The risk set thus included 1395 individuals at baseline in the EDSP study, with 5580 observations over the follow-up assessments, and 6603 individuals at baseline in NEMESIS-2, yielding 20455 observations.

Models

Analyzing panel data using random intercept models may not be consistent; therefore, if unbiased estimation is essential, these models may not be suitable. However, random-effects models have the advantage of efficiency and the ability to model heterogeneous effects, and sometimes an answer with a small bias and higher precision may be more useful than an unbiased model with poor precision. Wooldridge indicates that, in practice, researchers often estimate both the random-effects (RE) model and the fixed-effects (FE) model, and then use the Hausman test to determine which model is more appropriate.[39,40] In the analysis of panel data (the analysis of data over time), the Hausman test can be used as a test for model misspecification, helping to choose between a fixed-effects model or a random-effects model. The null hypothesis is that the preferred model is random effects; the alternate hypothesis is that the model is fixed effects. The tests look to see if there is a correlation between the unique errors and the regressors in the model. The null hypothesis is that there is no correlation between the two. Interpreting the result from a Hausman test is as follows: if the P-value is small (less than 0.05), the null hypothesis can be rejected. Therefore, when the Hausman test is significant, the FE model should be used; otherwise, the RE model should be preferred.[39] Analyses were carried out in Stata 16[41] using the xtlogit module, yielding ORs and their 95% CIs, with the FE option (within-person fixed effect) and RE option (random-effects model), followed by the "hausman" module to compare FE and RE models. FE models were adjusted for the following time-varying variables: age (in years), life events (binary), other drug use (binary), and any DSM diagnosis (binary). RE models were adjusted for the same variables.

Planned Sensitivity Analyses

The sample consisted of a merger of 2 separate cohorts with slightly different ways of data collection, interviewing, and variable definition. For the FE model, this cannot act as a confounder as a study sample does not vary within persons. Nevertheless, a planned sensitivity analysis was carried out, calculating the association between prior cannabis use at t-1 and PE at t, separately for NEMESIS-2 and EDSP. For the RE model, a planned sensitivity analysis was carried out, calculating the association between prior cannabis use at t-1 and PE at t whilst additionally adjusting for sample.

Results

Sample characteristics are displayed in Table 1. Rates of cannabis use and psychotic experiences were, as predicted, given their adolescent age, higher in the EDSP sample. Thus, in the NEMESIS-2 sample, the prevalence of psychotic experiences and cannabis use at baseline, in

Table 1. Sample demographics of NEMESIS-2 study (Netherlands) and EDSP study (Germany)

	NEMESIS-2		EDSP		Total	
	Mean	SD	Mean	SD	Mean	SD
Age at baseline	44.3	12.5	15.1	1.1	42.8	16.7
Sex	*N*[a]	%	*N*[a]	%	*N*[a]	%
Male	9143	44.7	2856	51.2	11 999	46.1
Female	11 312	55.3	2724	48.8	14 036	53.9
Total	20 455	100	5580	100	26 035	100
Baseline educational level[a]						
High	7591	37.1	3076	55.1	10 667	41
Medium	6588	32.2	1548	27.7	8136	31.3
Low	6276	30.7	956	17.1	7232	27.8
Total	20 455	100	5580	100	26 035	100
T0–T3 Psychotic experiences						
No	19 280	94.3	3865	80.6	23 145	91.7
Yes	1175	5.7	930	19.4	2105	8.3
Total	20 455	100	4795	100	25 250	100
T0–T3 Cannabis use						
No	19 454	97.9	3802	81.3	23 256	94.8
Yes	412	2.1	873	18.7	1285	5.2
Total	19 866	100	4675	100	24 541	100
T0–T3 Other drug use						
0	19 648	96.1	5188	93	24 836	95.4
1	807	3.9	392	7.0	1,199	4.6
Total	20 455	100	5580	100	26 035	100
T0–T3 Life event						
No	10 711	52.4	2426	43.5	13 137	50.5
Yes	9744	47.6	3154	56.5	12 898	49.5
Total	20 455	100	5580	100	26 035	100
T0–T3 any 12-month diagnosis						
No	17 784	86.9	4368	78.3	22 152	85.1
Yes	2671	13.1	1212	21.7	3883	14.9
Total	20 455	100	5580	100	26 035	100

Highest academic achievement: high = at least higher secondary; medium = lower secondary; low = no/primary.
EDSP, Early Developmental Stages of Psychopathology Study; NEMESIS-2, Netherlands Mental Health Survey and Incidence Study-2.
[a]Number of observations clustered within individuals (participants were interviewed 4 times over time).

those aged under 20 years, was 16.2% and 8.9% (not in table), respectively, not dissimilar to the corresponding rates at baseline in the EDSP sample aged 14–17 years at baseline at, respectively, 25.8% and 6.1% (not in table). Tables 2 and 3 show that both cannabis use status and psychotic experiences status over time were sufficiently dynamic—ie, moving in and out of status over time—to allow within-person analyses.

Table 4 shows that the rate of incident psychotic experiences at timepoint *t* as a function of cannabis at timepoint *t*-1 was consistently higher for the group using cannabis at *t*-1. Table 5 shows the same with regard to psychotic experiences at *t*-1 predicting incident cannabis use at timepoint *t*.

Fixed- and Random-Effects Models of Cannabis-Psychosis Associations

Table 6 displays the unadjusted and adjusted longitudinal associations of cannabis at timepoint *t*-1 with psychotic experiences at timepoint *t* in the risk set of those without psychotic experiences at timepoint *t*-1 (top half; Table 6), and, vice versa, the unadjusted and adjusted longitudinal associations of psychotic experiences at timepoint *t*-1 with cannabis use at timepoint *t* in the risk set of those without cannabis use at timepoint *t*-1 (bottom half; Table 6).

For 3 of the 4 models, and for all adjusted models, the Hausman test comparing FE and RE models was significant, indicating that the FE model should be used. RE models showed bidirectionality—cannabis predicting psychotic experiences and vice versa psychotic experiences predicting cannabis use (Table 6). However, FE models showed that cannabis use predicted psychotic experiences—at greater effect sizes than the RE models, whereas the reverse did not hold. If anything, prior psychotic experiences appeared to protect against cannabis use at follow-up (Table 6).

Planned Sensitivity Analyses

The results of the adjusted FE model of prior cannabis use predicting psychotic experiences (comparable

Table 2. Transitions in cannabis use over time from any *t*-1 to *t* (ie, over any 1 consecutive wave), any *t*-2 to *t* (ie, over any 2 consecutive waves), and any *t*-3 to *t* (ie, over any 3 consecutive waves) in a combined sample of NEMESIS-2 study and EDSP study

		Transition from *t*-1 to *t*					Transition from *t*-2 to *t*					Transition from *t*-3 to *t*				
		Cannabis use *t*					Cannabis use *t*					Cannabis use *t*				
Cannabis use *t*-1		0	1	Total	Cannabis use *t*-2		0	1	Total	Cannabis use *t*-3		0	1	Total
No	*N*[a]	15 305	378	15 683	No	*N*[a]	9,404	426	9830	No	*N*[a]	4275	306	4581
	%	97.6	2.4	100.0		%	95.7	4.3	100.0		%	93.3	6.7	100.0
Yes	*N*[a]	278	362	640	Yes	*N*[a]	207	160	367	Yes	*N*[a]	157	48	205
	%	43.4	56.6	100.0		%	56.4	43.6	100.0		%	76.6	23.4	100.0
Total	*N*[a]	15 583	740	16 323	Total	*N*[a]	9,611	586	10 197	Total	*N*[a]	4432	354	4786
	%	95.5	4.5	100.0		%	94.3	5.8	100.0		%	92.6	7.4	100.0

[a]Number of observations clustered within individuals (participants were interviewed 4 times over time).

to adjusted FE model; Table 6; top half) separately by sample showed similar effect size for NEMESIS-2 (OR = 7.38, 95% CI: 0.60, 91.09) and EDSP (OR = 6.10, 95% CI: 1.80, 20.65). The results of the adjusted RE model of prior cannabis use predicting psychotic experiences (comparable to adjusted RE model; Table 6; top half), with additional adjustment for sample, revealed a small further reduction of the effect size of the adjusted RE model (OR = 2.04, 95% CI: 1.40, 2.96).

Discussion

Interpretation of Findings

In a within-person analysis of the association between cannabis use and psychotic experiences, we showed a significant divergence between the results of traditional random-effects models and within-person fixed-effects models. Random-effects models showed bidirectionality in that cannabis use predicted psychosis and, vice versa, psychosis predicted cannabis use, similar to previous work in this area.[6] However, the preferred within-person model showed a strong association between preceding cannabis use and later psychosis, but not the other way round. If anything, preceding psychosis appeared to be protective for later cannabis use. Although effect sizes were higher in the FE model, CIs were largely overlapping with those in the RE model.

The divergence between the FE and RE models is important, given the fact that hypotheses in mental health research, such as the link between cannabis use and psychosis, are posited almost exclusively at the *within-person* level, whereas conventional testing of the hypotheses relies almost exclusively on *between-person* or mixed approaches.[42] The reason for the divergence between the 2 models likely has to do with conceptual divergence of the association in the between-person part of the model, just as the association between heart rate and physical exercise. Thus, at the within-person level, prior cannabis use increases the risk of psychosis, whereas prior psychosis tends to reduce the probability of cannabis use. Thus, the fact that there was a weaker association between prior cannabis use and psychosis in the random-effects model (the result of both within-person and between-person effects) may be due to the fact that individuals with psychosis proneness tend to avoid cannabis use (as suggested by the FE model) so that, at the population level, cannabis use becomes less positively associated with psychosis.

Comparison With Previous Work

The sample in the current study was larger than previous work[4,5] and statistically compared within-effects and random-effects approaches, finding the former more appropriate, which is relevant in view of divergent results in relation to the self-medication hypothesis. It concurred in finding evidence for a within-person person association

Table 3. Transitions in psychotic experiences over time from any *t*-1 to *t* (ie, over any 1 consecutive wave), any *t*-2 to *t* (ie, over any 2 consecutive waves), and any *t*-3 to *t* (ie, over any 3 consecutive waves) in a combined sample of NEMESIS-2 study and EDSP study

	Transition from *t-1* to *t*					Transition from *t-2* to *t*					Transition from *t-3* to *t*			
	Psychotic experiences *t*					Psychotic experiences *t*					Psychotic experiences *t*			
Psychotic experiences *t*-1		No	Yes	Total	Psychotic experiences *t-2*		No	Yes	Total	Psychotic experiences *t-3*		No	Yes	Total
No	*N*[a]	14 967	608	15 575	No	*N*[a]	9250	423	9673	No	*N*[a]	4241	163	4404
	%	96.1	3.9	100.0		%	95.6	4.4	100.0		%	96.3	3.7	100.0
Yes	*N*[a]	1026	465	1491	Yes	*N*[a]	743	261	1004	Yes	*N*[a]	503	104	607
	%	68.8	31.2	100.0		%	74.0	26.0	100.0		%	82.9	17.1	100.0
Total	*N*[a]	15 993	1073	17 066	Total	*N*[a]	9993	684	10 677	Total	*N*[a]	4744	267	5011
	%	93.7	6.3	100.0		%	93.6	6.4	100.0		%	94.7	5.3	100.0

[a]Number of observations clustered within individuals (participants were interviewed 4 times over time).

Table 4. Incident psychotic experiences as a function of cannabis use at the preceding interview over the periods T0–T1, T1–T2, and T2–T3 in a combined sample of NEMESIS-2 study and EDSP study

	Prediction from T0 to T1					Prediction from T1 to T2					Prediction from T2 to T3			
	T1 psychotic experiences					T2 psychotic experiences					T3 psychotic experiences			
T0 cannabis use		No	Yes	Total	T1 cannabis use		No	Yes	Total	T2 cannabis use		No	Yes	Total
No	*N*[a]	5141	166	5307	No	*N*[a]	4797	236	5033	No	*N*[a]	4163	118	4281
	%	96.9	3.1	100.0		%	95.3	4.7	100.0		%	97.2	2.8	100.0
Yes	*N*[a]	238	13	251	Yes	*N*[a]	101	36	137	Yes	*N*[a]	139	21	160
	%	94.8	5.2	100.0		%	73.7	26.3	100.0		%	86.9	13.1	100.0
Total	*N*[a]	5379	179	5558	Total	*N*[a]	4898	272	5170	Total	*N*[a]	4302	139	4441
	%	96.8	3.2	100.0		%	94.7	5.3	100.0		%	96.9	3.1	100.0

[a]Number of participants.

Table 5. Incident cannabis use as a function of psychotic experiences at the preceding interview over the periods T0–T1, T1–T2, and T2–T3 in a combined sample of NEMESIS-2 study and EDSP study

	Prediction from T0 to T1					Prediction from T1 to T2					Prediction from T2 to T3				
	T1 cannabis use					T2 cannabis use					T3 cannabis use				
T0 psychotic experiences		0	1	Total	T1 psychotic experiences		0	1	Total	T2 psychotic experiences		0	1	Total
No	*N*[a]	5190	77	5267	No	*N*[a]	4856	106	4962	No	*N*[a]	4126	101	4227
	%	98.5	1.5	100.0		%	97.9	2.1	100.0		%	97.6	2.4	100.0
Yes	*N*[a]	608	39	647	Yes	*N*[a]	282	18	300	Yes	*N*[a]	232	36	268
	%	94.0	6.0	100.0		%	94.0	6.0	100.0		%	86.6	13.4	100.0
Total	*N*[a]	5798	116	5914	Total	*N*[a]	5138	124	5262	Total	*N*[a]	4358	137	4495
	%	98.0	2.0	100.0		%	97.6	2.4	100.0		%	97.0	3.1	100.0

[a]Number of participants.

Table 6. Cannabis-psychosis causal hypothesis and cannabis-psychosis self-medication hypothesis: within-person fixed-effect model compared with random-effects model in a combined sample of NEMESIS-2 study and EDSP study

Predicted outcome	Model	Adjustment[b]	OR	95% LL	95% UL	*P*	Observations[c]	Individuals[c]	Hausman chi[2]	Hausman *P*
Incident[a] PE at *t* predicted by preceding cannabis use at *t*-1	FE	Not adjusted	9.16	3.23	25.97	0.000	827	375	1.01	.32
	RE		5.58	3.79	8.23	0.000	15 169	6240		
	FE	Adjusted	7.03	2.39	20.69	0.000	827	375	84.18	.000
	RE		2.29	1.60	3.28	0.000	15 169	6240		
Incident[a] cannabis use at *t* predicted by preceding PE at *t*-1	FE	Not adjusted	0.59	0.37	0.93	0.022	557	225	115.37	.000
	RE		4.27	3.23	5.64	0.000	15 671	6241		
	FE	Adjusted	0.59	0.21	1.71	0.33	557	225	95.23	.000
	RE		1.48	1.13	1.93	0.004	15 671	6241		

PE, psychotic experiences; FE, fixed-effects model; RE, random-effects model; 95% LL, 95% CI lower bound; 95% UL, 95% CI upper bound; Hausman, Hausman test comparing FE with RE model.
[a]Excluding individuals with psychotic experiences, respectively, cannabis use at preceding interview wave.
[b]Adjusted for age, life events, other drugs use, and any DSM diagnosis.
[c]Observations are clustered within individuals, given repeated measurements over time.

from cannabis to psychosis but not the other way round. One of the studies, similar to ours, reported a negative association between psychotic symptoms and subsequent cannabis use.[4] Relative risk effect sizes in previous work ranged from 2 to 5, not much different from reported effect sizes here. The fact that our effect sizes were somewhat higher may be related to the fact that we, having a larger sample, were able to model true incident outcomes, whereas previous work adjusted for baseline status of the outcome.[4,5]

Implications for Psychiatric Epidemiology

All time-varying environmental risks associated with mental health outcomes are amenable to within-person designs. For example, obstetric complications can be studied following multiple pregnancies over time and comparing pregnancies with and without complications within the same woman. Life events, drug use, social circumstances, urban environment, and other dynamically changing environmental exposures have only rarely been examined in a within-person design. Our findings suggest that increased reliance on within-person designs may be in order for investigating time-varying environmental factors.

Limitations

While fixed-effect models do not suffer from omitted variable bias, they have low power as only individuals with within-person changes in exposure/outcome status over time are informative. Although we showed that the sample was sufficiently enriched with these dynamic changes in exposure and outcome, the within-person analysis of the cannabis-psychosis association was carried out in 827 observations pertaining to 375 individuals, whereas the random-effects analysis was carried out in 15 169 observations pertaining to 6240 individuals

(Table 6). As a result, CIs were wider for the fixed-effect analysis results. In addition, fixed-effect analyses may still be confounded by time-varying factors, not all of which may have been captured in the current analyses. For example, high collinearity between cannabis and tobacco smoking did not allow for the control of tobacco smoking, which has been suggested as a potential risk factor for psychosis even though its psychoactive effects do not include psychosis.

Attenuated psychotic states, the main component of "clinical high risk" states, are the focus of much research focused on early intervention and prevention.[8–11] The current results, therefore, contribute to this rapidly developing area of research. As hypotheses were examined at the level of attenuated psychotic experiences and not clinical psychosis, results may not be generalizable to the full clinical syndrome. However, attenuated psychotic experiences show temporal, genetic, and broader etiological continuity with clinical psychosis[43–45]—which is why they are commonly used to investigate genetic and nongenetic hypotheses regarding the psychosis phenotype, given evidence that they pertain to the same spectrum as the psychotic syndrome, just as anxiety and depression phenotypes are thought to represent spectrum phenotypes with a half-normal distribution in the general population.[44]

Acknowledgments

The authors have no conflicts of interest to declare

Funding

NEMESIS-2 was supported by the Ministry of Health, Welfare and Sport, with supplementary support from the Netherlands Organization for Health Research and Development (ZonMw). The EDSP is funded by the German Ministry of Research and Education (BMBF) as part of the Addiction Research Initiative (01EB94056). This work was supported by the European Community's Seventh Framework Program under grant agreement no. HEALTH-F2-2009-241909 (Project EU-GEI).

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