Non-replication of interaction between cannabis use and trauma in predicting psychosis

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Dear Editors,

Cannabis use is considered a component cause of psychotic disorder interacting with genetic and environmental risk factors in increasing psychosis risk (Henquet et al., 2008). Recently, two cross-sectional and one prospective study provided evidence that cannabis use interacts additively with trauma to increase psychosis risk (Harley et al., 2010; Houston et al., 2008; Konings et al., in press). In an attempt at further replication, we examined prospective data from the German Early Developmental Stages of Psychopathology (EDSP) study (Lieb et al., 2000; Wittchen et al., 1998b).

The EDSP study collected data on the prevalence, incidence, risk factors, comorbidity, and course of mental disorders in a random, representative population sample of adolescents and young adults in the general population (Lieb, et al., 2000; Wittchen, et al., 1998b). Individuals were assessed three times (at T0, T2, and T3) over a 10-year follow-up period. More details on the sampling, representativeness, instruments, procedures, and statistical methods of the EDSP Study sample have been presented elsewhere (Lieb, et al., 2000; Wittchen, et al., 1998b). Data on psychotic symptoms, cannabis use and trauma were acquired with the computerized version of the Munich-Composite International Diagnostic Interview (DIA-X/M-CIDI) (Wittchen et al., 1998a), an updated version of the World Health Organization's CIDI version 1.2 (Robins *et al.*, 1988). At T0, the DIA-X/M-CIDI lifetime version was used. At each of the follow-up assessments, participants applied the interval version, covering the period of assessment from the last interview until the next. Data on positive psychotic symptoms were collected at T2 (lifetime version, representing lifetime experience of symptoms) and T3 (interval version, representing symptoms that occurred over the T2-T3 period). Presence of positive psychotic experiences was broadly defined as any rating of 'present' on any of the DIA-X/M-CIDI core psychosis items. All items were dichotomously rated as 'absent' or 'present'. Cannabis use was assessed at all three assessments. Conform previous analyses (Kuepper et al., 2011), cannabis use at T0 was defined

as lifetime use of cannabis of five times or more and cannabis use at T2 was defined as use of cannabis of five times or more since T0. Trauma was assessed at T0 and was dichotomously defined as having experienced any of the following events at least once lifetime: war experiences, physical threats or attacks, rape, sexual abuse, natural disasters, serious accidents, kidnapping and hostage-taking, and witnessing any of the aforementioned events.

Data were analyzed using STATA, release 11.1 (StataCorp, College Station, TX). Associations were expressed as odds ratios (OR) derived from logistic regression models. Interaction between T2 cannabis use and trauma was calculated under an additive model (Darroch, 1997), using the BINREG procedure in STATA yielding risk differences (RD), followed by calculation of the appropriate linear combinations from the model with the interaction, using the STATA LINCOM command. To ensure prediction of strictly incident psychotic symptoms over the T2-T3 follow-up period, all individuals who had reported lifetime psychotic experiences at T2 were excluded from the analyses. Analyses were adjusted for the following confounding risk factors: age (in years), sex (0=female, 1=male), socio-economic status (lower, middle, upper, other), cannabis use at baseline, use of other drugs at baseline (including psychostimulants, sedatives, opiates, cocaine, phencyclidine and psychedelic drugs), and urbanicity, defined dichotomously as living in the city of Munich ('urban', 4061 persons per square mile) or in the rural surroundings ('rural', 553 persons per square mile) at the time of inclusion.

We analyzed data of 1923 individuals of which 926 (48.2%) were men. Mean age was 18.3 years (SD = 3.3 years) at T0, 21.8 (SD = 3.4 years) at T2 and 26.6 (SD = 3.5 years) at T3. There was no evidence that trauma moderated the association between T2 cannabis use and incident psychotic symptoms over the T2-T3 period (see table 1 for statistics). The interaction remained small and non-significant when examining a more stringent outcome criterion, defined as having experienced at least two psychotic symptoms, and when examining the influence of having been exposed to at least two or three traumatic events, respectively. In order to strictly predict incident psychotic symptoms over the T2-T3 period, the above described analyses excluded all individuals

with lifetime pre-existing psychotic symptoms as assessed at T2. Accordingly, the remaining group of subjects exclusively consisted of individuals who had not developed any psychotic symptoms by the time of the T2 assessment, possibly constituting a relatively resilient subgroup. However, the interaction remained non-significant also when analyzing the whole cohort (-1.3% adjusted difference in risk, 95% CI: -11.1- 8.4, $p = 0.782$).

Opposed to what was hypothesized and in contrast to previous findings (Harley, et al., 2010; Houston, et al., 2008; Konings, et al., in press), the current analyses did not provide evidence for interaction between cannabis use and trauma in increasing psychosis risk. This may be due to sampling variation, or alternatively, the relatively long follow-up between T2 and T3 was insensitive to this type of analysis. More work in the area of environment-environment interactions in predicting psychosis is necessary.

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Table 1. Interaction between cannabis use and trauma

T2 cannabis use	Number with psychotic symptoms*	Number without psychotic symptoms*	% Psychotic symptoms	Risk difference		Test for overall interaction [#]	
				<i>Unadjusted</i>	<i>Adjusted^l</i>		
<i>Without trauma</i>							
<i>No</i>	127	1137	11.2%	9.6%	4.3%	-0.1% adjusted difference in risk, 95%CI: -10.4- 10.4, <i>p</i> = 0.994	
<i>Yes</i>	51	245	20.8%		95%CI: -0.9-9.4, <i>p</i> = 0.105		
<i>With trauma</i>							
<i>No</i>	35	231	15.2%	7.6%	4.2%		
<i>Yes</i>	18	79	22.8%		95%CI: 5.3-13.8, <i>p</i> = 0.386		

Note. Individuals with T2 lifetime psychotic experiences were excluded from the analyses.

*Assessed at T3 as follows: any rating of ‘present’ on any of the DIAX/M-CIDI core psychosis items.

¹ Adjusted for age, gender, socio-economic status, baseline cannabis use, use of other drugs, and urban environment.

[#] Tests whether risk difference in exposure group (‘with trauma’) is significantly greater than risk difference in non-exposure group (‘without trauma’).