1997). Although the current cross-sectional data cannot distinguish cause and effect, the presented results are applicable irrespectively of the question of causality. If cannabis plays a causative role in the psychotic disorders, the finding that very early and heavy use increases this effect is highly relevant and suggestive for a specific neurobiological interplay at puberty. If however the relationship should be reciprocal, the results point out that early and heavy cannabis are clinically meaningful markers of vulnerability to serious future psychopathology. A history of cannabis use before the age of twelve years clearly predisposes to distressing symptoms of psychosis, especially positive symptoms.

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AGE AT ONSET OF PSYCHOSIS IN PATIENTS WITH SCHIZOPHRENIA: EVIDENCE FOR A SEX-DEPENDENT INTERACTION BETWEEN BDNF VAL66MET GENOTYPE AND CANNABIS USE

Jeroen Decoster[1,2], Jim van Os[2,3], Gunter Kenis[2], Cécile Henquet[2], Joseph Peuskens[1], Marc De Hert[1], Ruud van Winkel[1,2]
[1]*University Psychiatric Centre, Catholic Universtity, Leuven, Kortenberg, Belgium*; [2]*Department of Psychiatry and Neuropsychology, South Limburg Mental Health Research and Teaching Network, EURON, Maastricht University Medical Centre, Maastricht, Netherlands*; [3]*Division of Psychological Medicine, Institute of Psychiatry, Londen, United Kingdom*

Background: Discovering modifiable predictors for age at onset may help to identify predictors of transition to psychosis in the 'at-risk mental state'. Previous studies inconsistently reported main effects of sex, BDNF Val66Met and cannabis, suggesting more complex models may be required. A sex-specific model of gene-environment interaction between BDNF Val66Met and cannabis use, affecting age at onset of psychosis, was hypothesized.
Methods: BDNF Val66Met and cannabis use before illness onset were assessed in a sample of 587 patients with schizophrenia. Survival analyses were fitted with time from birth to age at first admission as indicator for survival time.
Results: Mean age at onset was 24.6 years (SD 7.2, range 14.0-62.9). Sex (Log rank $\chi2(1) = 40.1$, $p < .001$), BDNF Val66Met genotype (Log-rank $\chi2(1) = 3.8$, $p = .050$) and cannabis use (Log-rank $\chi2(1) = 22.1$, $p < .001$) were significantly associated with age at onset in univariable Log-rank survival analyses. Multivariable Cox regression confirmed the association with sex (HR 1.58, 95% CI 1.30 – 1.92, $p < .001$), cannabis use (HR 1.32, 95% CI 1.03 – 1.70, $p = .028$) and BDNF genotype (HR 1.24, 95% CI 1.04 – 1.48, $p = .018$) controlled for each other and the effects of other drug use (cocaine, stimulants, phencyclidine, psychedelics and opiates). Male patients, BDNF Met-carriers and cannabis users had an earlier onset of 3.7 years, 1.2 years and 2.7 years, respectively. Besides, age at onset was significantly predicted by the frequency of cannabis use in the most intense period (HR 1.27, 95% CI 1.05 – 1.54, $p = .016$) and a younger age at first use of cannabis (HR 1.41, 95% CI 1.17 – 1.70, $p < .001$), as shown by multivariable models controlling for the effects of other drug use and sex. However, the above reported main effects cannot reliably be interpreted as a significant BDNF X cannabis X sex three-way interaction was also found (interaction $\chi2(1) = 4.99$, $p = .026$). In male patients, BDNF Val66Met (HR 1.97, 95% CI 1.45 – 2.68, $p < .001$) and cannabis (HR 2.10, 95% CI 1.57 – 2.79, $p < .001$) showed highly significant main effects without evidence for gene-environment interaction (interaction $\chi2(1) = 0.04$, $p = .846$). In female patients, cannabis use and BDNF Val66Met only decreased age at onset (with more than 7 years) when present in combination (interaction $\chi2(1) = 6.06$, $p = .014$).
Discussion: Sex, BDNF Val66Met and cannabis use are associated with age at onset of psychosis, but these associations cannot be interpreted without taking their interaction into account. Sex-specific effects of BDNF Val66Met genotype may help to explain individual differences in vulnerability for the effects of cannabis.

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CANNABIS AS CAUSE OF PSYCHOSIS: EFFECTS ON INCIDENCE AND PERSISTENCE OF PSYCHOTIC SYMPTOMS

Rebecca Kuepper[1], Jim van Os[1,3], Inez Myin-Germeys[1], Roselind Lieb[4], Hans-Ulrich Wittchen[4,5], Cecile Henquet[1,2]
[1]*Department of Psychiatry and Neuropsychology, South Limburg Mental Health Research and Teaching Network, EURON, Maastricht University, Maastricht, Netherlands*; [2]*Mondriaan Zorggroep, Division Addiction Care, South Limburg, Netherlands*; [3]*Division of Psychological Medicine, Institute of Psychiatry, London, United Kingdom*; [4]*Clinical Psychology and Epidemiology Unit, Max Planck Institute of Psychiatry, Munich, Germany*; [5]*Institute of Clinical Psychology and Psychotherapy, Technical University, Dresden, Germany*

Background: Adolescent cannabis use has been shown to increase the risk for the later development of psychotic symptoms. There is still debate, however, whether this association is causal or follows the so-called self-medication hypothesis. Further, it is unknown whether cannabis use impacts on persistence rates of psychotic symptoms.
Methods: Prospective data from the German Early Developmental Stages of Psychopathology (EDSP) study were analyzed ($N = 1920$, age at baseline 14 to 24 years). Substance use and psychotic symptoms were assessed at baseline and at follow-up (t2 four years later) and again at t3 (eight years later), by means of the Munich Composite International Diagnostic Interview. Logistic regression analyses were conducted to investigate the effects of cannabis use on later risk for incidence and persistence of psychotic symptoms. Persistence was defined as expressing psychotic symptoms at both follow-up occasions (t2 and t3).
Results: Cannabis use at t2 significantly increased the risk for psychotic symptoms at t3, in individuals who were cannabis naïve at baseline and had no sign of psychotic symptoms at t2 (OR = 1.88; 95% CI: 1.13-3.14, $p = 0.018$). The effects were independent of age, gender, socio-economic status, urbanicity and childhood trauma and could not be explained by self-medication (i.e. psychotic symptoms at t2 predicting cannabis use at t3). Occasional cannabis use (i.e. cannabis use at either t0 or t2) was associated with an increased risk of persistence of psychotic symptoms, independent of age, gender, socio-economic status, urbanicity and childhood trauma (OR = 1.67, 95% CI: 1.03-2.67, $p = 0.037$). The risk of persistence of psychotic symptoms was much higher for those, who reported continuous cannabis use (i.e. cannabis use at t0 and t2, OR = 2.25, 95% CI: 1.19-4.25, $p = 0.013$). Again, this was independent of confounding.
Discussion: The present study is in line with the notion that cannabis acts as an independent risk factor for the development of psychotic symptoms. The results show that continuous use of cannabis leads to a greater risk of persistence of those symptoms. This suggests that environmental risk factors such as cannabis use impact on psychosis risk via a process of sensitization (i.e. repeated exposure to an environmental stressor leads to progressively greater behavioral responses over time).

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