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Cannabis use disorder and age at onset of psychosis — A study in first-episode patients

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ABSTRACT

Introduction: Age at onset of psychosis (AAO) may be younger in patients with cannabis use disorders (CUD) compared to those without CUD (NCUD). Previous studies included CUD co-morbid with other substance use disorders (SUD), and many did not control for confounders.
Methods: Controlling for relevant confounders, differences in AAO between patients with and without CUD excluding those with any other SUD were analyzed in a large representative file audit of 625 first-episode psychosis (FEP) patients (age 14 to 29 years) admitted to the Early Psychosis Prevention and Intervention Centre in Melbourne, Australia.
Results: Three quarters of the 625 FEP patients had a CUD. Cannabis use started before psychosis onset in 87.6% of patients. AAO was not significantly different between CUD (without other SUD, n = 201) and NCUD (n = 157). However, AAO was younger in those with early CUD (starting age 14 or younger) compared to NCUD ($F(1) = 5.2$; $p = 0.024$; partial $\eta^2 = 0.026$). Earlier age at onset of cannabis use predicted earlier age at onset of psychosis ($\beta = -0.49$, R^2-change = 0.25, $p < 0.001$).
Conclusion: Only CUD starting age 14 or younger was associated with an earlier AAO at a small effect size. These findings suggest that CUD may exert an indirect effect on brain maturation resulting in earlier AAO potentially only in cannabis sensitive subjects.

1. Introduction

Previous studies support the role of cannabis as a risk factor for psychosis. Arseneault et al. (2004) systematically reviewed all prospective epidemiological studies. The authors concluded that cannabis use confers an overall twofold increase in the relative risk for later schizophrenia. Notably, the effect of cannabis exposure on the presence of psychotic symptoms was reported to be significantly stronger when exposure occurs in early adolescence (Arseneault et al., 2002; Konings et al., 2008) and when cannabis use was persistent (Kuepper et al., 2011). Konings et al. (2008) used age 14 as cut-off for early cannabis exposure. Interestingly, the literature also suggests that age at onset of psychosis (AAO) is younger in patients abusing cannabis compared to those who do not, on the basis of data stemming from retrospective studies conducted in adult-onset multiple- or first-episode psychosis (Large et al., 2011).

Several explanations have been suggested for the relationship between cannabis use and psychosis: First, there is evidence that the endocannabinoid system plays an important role in brain developmental processes in those brain regions (prefrontal cortex, limbic structures and hippocampus) and neurotransmitter systems (GABAergic and dopaminergic transmission), which are pathophysiologically relevant to schizophrenia (Malone et al., 2010). Thus, a causal link between cannabis use and the emergence of psychosis and potentially also between early cannabis use and a younger AAO is intuitively likely, particularly if early cannabis use or abuse interferes with brain developmental processes in adolescence. A second hypothesis proposes that cannabis use causes psychosis by means of gene environment interaction (Caspi et al., 2005). For example, the study by Caspi et al. (2005) found that a functional polymorphism in the catechol-O-methyltransferase (COMT) gene moderated the influence of adolescent cannabis use on developing adult psychosis. A third hypothesis postulates that the earlier AAO in cannabis users may be the result of factors unrelated to cannabis such as gender or pre-morbid adjustment. The respective studies, however, report inconsistent results (Barnes et al., 2006; Gonzalez-Pinto et al., 2008; Sevy et al., 2010).

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Limitations of many previous studies on the link between cannabis use and AAO included (Zammit et al., 2008): (i) small sample sizes; (ii) failure to report effect sizes; (iii) failure to control for relevant confounders, and (iv) lack of representativeness of samples due to an informed consent procedure, which patients with severe and/or severe psychoses are more likely to refuse (Friis et al., 2003; Wade et al., 2006).

To date, no study explored AAO differences between those with cannabis use disorders (CUD) only, excluding co-morbidity with other substance use disorders (SUD), and those without CUD. Therefore, based on a large cohort of 625 adolescent and adult first episode psychosis patients (age 14–29 years), we examined differences in AAO between patients with lifetime CUD only (n = 201) and patients without CUD (n = 158), taking into account the potential confounding effect of gender and/or premorbid functioning. Based on the literature, we expected that (i) AAO would be younger in patients with CUD only compared to those without CUD (NCUD) (Large et al., 2011) and (ii) the effect of CUD on younger AAO would be even more pronounced if early CUD (cannabis use starting at age 14 or younger) were compared to NCUD.

2. Methods

2.1. Context and sample

This is a retrospective file-audit study. Data were sourced from the First Episode Psychosis Outcome Study (Conus et al., 2007). The initial sample comprised a population-based cohort of 786 first-episode psychosis (FEP) patients, consecutively admitted to the Early Psychosis Prevention and Intervention Centre (EPPIC) in Melbourne, Australia, between 1998 and 2000. EPPIC covered a catchment area of approximately 880,000 people, and had a mandate to offer treatment to all FEP patients aged 14–29. As such, this clinical sample is approaching epidemiological representativeness for urban settings. The EPPIC program comprises a comprehensive early intervention treatment program, with a usual episode of care of 18 months, which encompasses extensive assessments. Each patient is assigned to a core team, who treats the patient across settings and makes entries into the chart (McGorry et al., 1990a,b).

Of the 786 patients admitted to EPPIC, 82 files (10%) had been sent to other services. The excluded patients did not differ in available demographic characteristics (age and gender) and diagnostic distribution at baseline. 57 (8.1%) of the remaining 704 patients were excluded from the study due to a final diagnosis of non-psychotic disorder, substance-induced psychosis or psychosis due to general medical conditions. Further, 11 (1.6%) patients were excluded due to missing data regarding CUD and 8 (1.1%) due to missing data regarding AAO. Further, three outliers regarding AAO (age 8.21, 8.36 and 9.97) were detected in preliminary analyses and excluded. Out of the remaining 625 patients, 267 (42.7%) were excluded due to CUD co-morbid with other SUD. Data from 358 FEP patients with CUD only (n = 201) or NCUD (n = 157) was analyzed.

2.2. Procedure

All information on pre-treatment, baseline (at the time of admission to EPPIC), treatment and outcome variables for each patient treated at EPPIC is systematically documented in one standardized file including information over the treatment period as assessed with the Royal Park Multi-diagnostic Instrument for Psychosis (McGorry et al., 1990a,b). Using a systematic comprehensive approach (Early Psychosis File Questionnaire (EPFQ)) (Conus et al., 2007), all charts were rated by two experienced psychiatrists well acquainted with the EPPIC clinical service and treatment of young patients with FEP (ML & PC). A local ethics committee granted approval for this 'non-informed consent' file audit study allowing for the unselected inclusion of patients.

2.3. Assessment of diagnoses

Clinical diagnoses (psychoses and SUD including CUD) according to DSM-IV criteria (APA, 2000) were based on the consensus of trained clinicians of the specialized assessment and crisis intervention team following an intensive diagnostic process within the first 6 weeks after entry into service. The main investigators (ML & PC) re-assessed all information available in charts with respect to baseline diagnoses. Validity of the file audit diagnoses was established by the following procedure: Between 1998 and 2000, 230 of the 786 patients treated at EPPIC had been included in prospective trials. Their main and co-morbid diagnoses were defined within 6 weeks of admission using the Structured Clinical Interview for DSM-IV (SCID-I/P; Ventura et al., 1998). The SCID and file audit diagnoses of 115 patients randomly selected within this sample of 230 were compared. The calculated kappa values revealed a very good concordance for both psychosis diagnoses (kappa = 0.80) and SUD diagnoses (kappa = 0.74).

2.4. Assessment of cannabis use disorders

The prevalence of lifetime CUD, i.e., cannabis abuse or dependency according to DSM-IV criteria, as well as the age at onset of cannabis use was assessed with the Drug and Alcohol Assessment Schedule (DAAS) (McGorry et al., 1990a,b) during the first 6 weeks after service entry. Any cannabis use pattern, which did not fulfill the DSM-IV criteria for cannabis use disorders, was not assessed. The principal investigators (ML and PC) extracted this data from the files. As for some patients, the existence of lifetime CUD became only known during treatment, the CUD classification of the study was not based on DAAS results alone but on all available information in the files collected throughout the 18-month treatment period at EPPIC (Schimmelmann et al., in press). The calculated kappa value revealed a good concordance between prospectively assessed SUD diagnoses and those from the file-audit used in this study (kappa = 0.74).

2.5. Assessment of duration of untreated psychosis (DUP) and age at onset

DUP was defined as age at entry into EPPIC subtracted by age when first sustained positive psychotic symptoms started (Schimmelmann et al., 2007, 2008). Clinicians at EPPIC were trained to determine DUP with patients and their relatives. In several cases, this date was modified in the file over the course of treatment on the basis of new information being gathered: For example, as patients became clinically more stable and therefore more able to reflect on symptoms' onset, they provided further details on the evolution of symptoms allowing for a more accurate estimate of DUP. The main investigators made a final decision based on all available data in the file.

2.6. Assessment of pre-treatment variables

Pre-treatment characteristics extracted from the files included the highest premorbid functioning according to the Global Assessment of Functioning Scale (GAF; APA, 1994), as the commonly used Premorbid Adjustment Scale was too complex to reliably extract data from files. Inter-rater reliability (ML and PC) was established for premorbid GAF-scores (kappa = 0.88).

2.7. Data analysis and statistical tests

Descriptive statistics were applied to compare CUD and NCUD in terms of gender and pre-treatment characteristics using Mann–