Schizophrenia Research xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

The effect of drug use on the age at onset of psychotic disorders in an Australian cohort

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ARTICLE INFO

Article history:
Received 17 December 2013
Received in revised form 14 March 2014
Accepted 2 April 2014
Available online xxxx

Keywords:
Schizophrenia
Causality
Cannabis
Amphetamine
Psychosis

ABSTRACT

Background: We aimed to examine the association between illicit substance use and age at onset in psychotic disorders in an Australian cohort.
Methods: Retrospectively acquired information on substance use during the year prior to illness onset was collected from 1642 participants enrolled in the Australian National 2010 Survey of High Impact Psychosis study (SHIP), with an ICD-10 diagnosis of schizophrenia spectrum or affective psychosis. Latent class analysis was performed according to illicit substance use, using age as an active covariate; identified classes were subsequently validated. Cox regression was used to examine the independent contribution of the identified substance use classes and several confounding variables to the prediction of age at onset of psychosis.
Results: Three classes according to substance use were identified: non-users ($n = 803$), cannabis predominant users ($n = 582$), and polysubstance users ($n = 257$). For participants with schizophrenia spectrum disorders, cannabis predominant users had a higher hazard of earlier age at onset than for non-users (adjusted HR = 1.38, 95% CI = 1.2–1.6); polysubstance users had an even higher hazard (adjusted HR = 1.95, 95% CI = 1.5–2.4). In contrast, for participants with affective psychosis, cannabis predominant users (adjusted HR = 1.10, 95% CI = 0.8–1.4) and polysubstance users (adjusted HR = 0.87, 95% CI = 0.6–1.3) did not have a higher hazard of earlier age at onset compared with non-users.
Conclusions: Illicit substance use in the 12 months prior to psychosis onset has a differential effect on age at onset in schizophrenia spectrum and affective psychotic disorders. Our findings are compatible with the notion that illicit drugs bring forward age at onset in schizophrenia spectrum disorders but not affective psychotic disorders.
Published by Elsevier B.V.

1. Introduction

There is much debate regarding the association between substance use and age at onset (AAO) in psychosis, with a recent meta-analysis reporting an earlier mean AAO in samples with more cannabis users, and arguing in favor of a causality hypothesis (Large et al., 2011) (i.e., that the illness is precipitated by cannabis, possibly in those predisposed to develop psychosis) (Henquet et al., 2006; Stefanis et al., 2004). Others maintain that the association is likely to be spurious (i.e., younger participants are more likely to use cannabis) (Wade, 2005). Consistent with the hypothesis that cannabis may bring forward psychosis onset, recent studies have demonstrated that age of cannabis initiation was associated with AAO of psychotic symptoms in high risk individuals (Dragt et al., 2012) and directly and linearly associated with age at prodrome onset and AAO in schizophrenia spectrum disorders (SSD) (Galvez-Buccollini et al., 2012; Leeson et al., 2012; Stefanis et al., 2013). However, the complex temporal relationship between substance use and psychotic symptoms in the premorbid period defies simple interpretations that are further hampered by a plethora of confounding factors, including uncertainties regarding the effect of comorbid substance use in addition to cannabis, and the specificity or not of these effects to SSD.

Several studies have examined the association between number of illicit substances consumed and AAO in SSD, and have reported disparate findings (Barnes et al., 2006; Gonzalez-Pinto et al., 2008; Dekker et al., 2012; Power et al., 2012). For instance, Dekker et al. (2012)

Abbreviations: AAO, age at onset; AIC3, Akaike information criterion 3; APD, affective psychotic disorders; BIC, Bayesian information criterion; DIP, Diagnostic Interview for Psychosis; ICD-10, International Classification of Diseases Version 2010; LCA, latent class analysis; LSD, lysergic acid diethylamide; OPCRIT, Operational Criteria for Psychosis; SSD, schizophrenia spectrum disorders; SHIP, Survey of High Impact Psychosis.

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http://dx.doi.org/10.1016/j.schres.2014.04.003
0920-9964/Published by Elsevier B.V.

examined the effect of substance use in the 12 months prior to interview and over the lifetime, and reported that cannabis use had a similar effect compared with cannabis plus another illicit substance. However, we recently reported that the consumption of illicit substances in addition to cannabis (specifically in the 12 months prior to onset) predicted an earlier AAO by approximately one additional year in schizophrenia (Power et al., 2012); this remained significant after controlling for mean duration of illness, and was independent of family history of schizophrenia and sex. There were a number of limitations imposed on this study by sample size, such that replication is warranted.

Few studies have examined the association between substance use (namely alcohol and cannabis) and AAO in affective psychotic disorders (APD) (Strakowski et al., 2005; Fossey et al., 2006; Lin et al., 2006; Strakowski et al., 2007; Ringen et al., 2008; Lagerberg et al., 2011). Although Lin et al. (2006) did not differentiate between the types of substance used, they reported an increased risk of substance abuse for patients with younger onset of bipolar disorder. Other authors, however, have reported a later onset for patients who abuse substances prior to onset of bipolar disorder (Strakowski et al., 2005; Fossey et al., 2006; Strakowski et al., 2007), while excessive cannabis use in the period prior to illness onset has been associated with earlier onset in 151 patients with bipolar disorder (types I and II) (Lagerberg et al., 2011). While methodological differences may explain these discrepancies, Lagerberg et al. (2011) also hypothesize that differences in the sequence of onset of bipolar disorder and onset of substance use disorder may have a bearing on age at onset of illness. Nonetheless, these disparate findings suggest that the association between premorbid substance use and AAO of APD warrants further investigation.

Responding to conflicting findings regarding the premorbid effect of substance use on the AAO of SSD and APD, we set out to investigate this association in a large sample of people with psychosis in which information on substance use in the 12 months prior to onset of illness was available. We hypothesized that cannabis consumption in the 12 months prior to illness onset would lead to an earlier AAO of both SSD and APD. We also aimed to independently replicate our initial finding that illicit substance use in addition to cannabis in the 12 months prior to onset would have an additive effect on AAO in schizophrenia, and to examine whether these findings were consistent for SSD and APD.

2. Experimental/materials and methods

2.1. Participants

Participants were selected from the 2010 Australian SHIP (Survey of High Impact Psychosis), the methods of which have been described elsewhere (Morgan et al., 2012; Stefanis et al., 2013). In brief, participants were recruited from across seven sites in Australia, employing a two-phase sampling design. In phase 1, screening for psychosis was conducted in participants aged 18–64 in contact with public mental health services and non-government organisations supporting people with mental illness. Of the 7955 who screened positive for psychosis, 1825 were randomly selected and engaged in assessment (phase 2); participants provided written informed consent. From the 1825 participants who were able to be interviewed, those who did not meet full criteria for an ICD-10 psychotic disorder in phase 2 were excluded ($n = 183$), leaving a total of 1642 participants with an established ICD-10 diagnosis of SSD (schizophrenia, schizoaffective, delusional and other non-organic psychotic disorder) or APD (bipolar disorder, depressive disorder with psychotic features).

2.2. Measures — diagnostic algorithm

Participants in phase 2 were assessed using the DIP (Diagnostic Interview for Psychosis), a standardized semi-structured interview for psychosis (Castle et al., 2006). The DIP is comprised of a number of modules (demography and social functioning, diagnostic, service utilization). The diagnostic module (DIP-DM) follows the structure of the Operational Criteria for Psychosis (OPCRIT) (McGuffin et al., 1991), a 90-item checklist which allows the examiner to rate symptoms in a number of domains (present state, past year, and lifetime). Diagnostic classification of cases was made using the OPCRIT diagnostic computer algorithm (McGuffin et al., 1991). In addition, the DIP includes items on substance use (alcohol, tobacco, cannabis, amphetamines, LSD, cocaine, ecstasy), including frequency of use in the 12 months prior to onset of psychosis. Participants were categorized as either substance-users (ranging from "daily use" to "used less frequently than once per month"), or substance non-users (if they reported "no use"). The DIP also includes items regarding the use of alcohol to determine ICD-10 classifications for alcohol abuse and dependence.

2.3. Definition of AAO

AAO was determined after interviewing the participant, and recorded to the nearest year (defined as the earliest age medical advice was sought for psychiatric reasons, or that any psychiatric symptom diagnostic of psychotic or major affective illness began to cause subjective distress or impair functioning). If there were no clear symptoms described, age at first hospital admission was recorded.

2.4. Statistical analysis

To investigate whether there existed classes according to illicit substance use within the SHIP ($n = 1642$), latent class analysis (LCA) was performed using illicit substance use (cannabis, amphetamine, cocaine, LSD, ecstasy) in the 12 months prior to onset of illness as nominal indicators. We used age at interview as an active covariate, thus allowing participants' age to influence the classification probabilities; age categories were determined impartially using the binning procedure with three equal percentiles based on scanned data (age at interview $\leq$32, 33–43, and $\geq$44 years). The optimal LCA solution was determined by identifying a point of a convincing convergence of various fit indices. The identified classes were then described using one way analysis of variance or Pearson's chi-square test (χ^2). Analyses were performed using IBM SPSS (version 20) and Latent GOLD (version 4.0.4).

Based on the substance-using age-adjusted classes of participants identified and externally validated in LCA, we then sought to determine the effect of substance-using status on AAO in both SSD and APD. We used Cox proportional hazards regression models to predict a status (event) variable, namely AAO of psychosis, using latent class membership as the principle predictor. We then investigated the possible influence of several confounding factors to adjust crude hazard rates. The cumulative hazard of AAO was determined and presented graphically according to illicit substance use for both SSD and APD.

3. Results

3.1. Demographic data

Table 1 illustrates the demographic data of SHIP participants. There were 1242 participants diagnosed with SSD, and 400 participants with APD. Additional data pertaining to further sociodemographic data, lifestyle variables, mental health profile, medications, service utilization, functioning and quality of life have been reported elsewhere (Morgan et al., 2012).

3.2. Classes according to substance use

The best-fitting model produced by the LCA according to substance use and using age as an active covariate was a three-class model: Class 1 ($n = 803$; 49%), Class 2 ($n = 582$; 35%) and Class 3 ($n = 257$; 16%). Inspection of the log likelihood statistic plot indicated that the optimal number of classes was three, being the most clinically parsimonious

Please cite this article as: Stefanis, N.C., et al., The effect of drug use on the age at onset of psychotic disorders in an Australian cohort, Schizophr. Res. (2014), http://dx.doi.org/10.1016/j.schres.2014.04.003