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Cannabis use, gender and age of onset of schizophrenia: Data from the ÆSOP study

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ABSTRACT

An earlier age of onset of schizophrenia has been identified as a poor prognostic indicator. The current study examines the interaction effect of gender and cannabis use on age of onset of schizophrenia and schizoaffective disorder. This research forms part of a two-centre epidemiological study of first-episode psychosis and included individuals with a diagnosis of schizophrenia or schizoaffective disorder and an age of onset between age 16 and 45. Kaplan–Meier curves and Cox proportional hazards regression were used to compare the effects of cannabis use and gender on age of first symptom of schizophrenia. Akaike's information criteria were used to find the model with the best fit to the data. Cannabis users had an earlier age of first symptom than non-users. There was an interaction with gender; the gender difference in age of onset was diminished in cannabis smokers compared with non-cannabis smokers. The model including cannabis use interacting with gender was the most parsimonious model, followed by cannabis use alone. The addition of other illegal drug use did not improve the model. Cannabis use is associated with an earlier age of onset of schizophrenia, and the gender difference in age of onset is reduced among cannabis smokers.

1. Introduction

A gender difference in age of onset of schizophrenia has been consistently reported and a recent meta-analysis has shown that males are on average 1.63 years younger when they first experience psychotic symptoms (Eranti et al., 2013). An earlier age of onset of schizophrenia has been associated with a poor prognosis, including greater cognitive and functional impairment, more severe symptoms, increased risk of relapse and re-hospitalisation, more days spent in hospital per year and less responsiveness to antipsychotics (DeLisi, 1992; Linszen et al., 1994; Rabinowitz et al., 2006; Rajji et al., 2009).

Cannabis use is common in those with a first episode of psychosis, although more prevalent in males than females (*e.g.* Addington and Addington, 2007; Donoghue et al., 2011; Larsen et al., 2006; Sevy et al., 2010). Cannabis use has been found to be associated with an earlier age of onset of schizophrenia with cannabis users developing the illness on average 2.70 years younger than non-cannabis users (Large et al., 2011). In further support of this relationship, an association has also been found between the age of initiation of cannabis use and the age of onset of schizophrenia (Leeson et al., 2012; Stefanis et al., 2013).

The gender difference that is seen in age of onset may be confounded by differential cannabis use in males versus females, especially in countries with a high prevalence of cannabis use, such as the UK. The current study aims to study the gender differential for age of onset of schizophrenia, in a large first episode study in the UK, and to test the hypothesis that the gender difference in age of onset is confounded by cannabis use.

2. Method

This research forms part of the Aetiology and Ethnicity of Schizophrenia and Other Psychoses (ÆSOP) study, a three-centre epidemiological study of first-episode psychosis that took place in Nottingham, Bristol and South East London, although the Bristol sample lacked data on substance use so was not included in the current study. Ethical approval for the research was granted by the local Research Ethics Committees. Full details of entry criteria and study design have

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been reported elsewhere (Fearon et al., 2006; Kirkbride et al., 2006) therefore only those details relevant to the current research will be included here.

All potential cases aged 16–64 who presented to mental health services with a first-episode of psychosis (ICD-10: F10–F29 and F30–F33) (WHO, 1992) between the years 1997 and 1999 were identified. All points of secondary mental health contact were monitored to identify all potential cases of first-episode psychosis. To further ensure that potential cases were not missed, a 'leakage' study was conducted using the methods of Cooper et al. (1987). This involved retrospectively scrutinising the electronic and paper information systems of mental health services to identify those patients who had been given a diagnosis of a psychotic syndrome. Case notes were reviewed and interviews with clinical staff were conducted to ensure these cases met the studies inclusion and exclusion criteria.

Diagnoses were assigned for each participant subsequent to completed data collection by consensus meetings. A vignette that summarised the presenting complaint was presented in addition to clinical information from the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) or the Item Group Checklist (IGC) (WHO, 1994) for those that refused interview. Only participants who were aged younger than 45 at onset of psychotic symptoms and received a consensus diagnosis of schizophrenia or schizoaffective disorder according to the ICD-10 (F20, F25) were included in this paper. This is because late onset of schizophrenia may represent a distinct sub-sample of the disorder characterised by less severe positive symptoms, better cognitive function, lower dose antipsychotics, better every day functioning and increased prevalence in women (Vahia et al., 2010). Since there is no agreement on the cut-off age for late onset schizophrenia, the current study included only those individuals with a first episode of schizophrenia/schizoaffective disorder presenting before age 45.

The onset of psychosis was defined as the presence, for 1 week or more, of one of the following psychotic symptoms: delusions, hallucinations, marked thought disorder, marked psychomotor disorder (other than simple retardation or acceleration), and bizarre, grossly inappropriate and/or disorganised behaviour with a marked deterioration in function, and will be referred to as the onset of psychotic symptoms in the current study. Data relating to date of onset of psychosis was collated from interviews with the patient, a close relative, and clinical notes using the Personal and Psychiatric History Schedule (PPHS) (Jablensky et al., 1992). The age at which a person first came into contact with secondary mental health services with the presence of psychotic symptoms as described above will be referred to as the age of first contact in the current study. Duration of Untreated Psychosis (DUP) was defined as the period of time from the onset of psychosis to first contact with mental health services for psychosis.

Information on drug use before the first presentation to mental health services was collected using three sources: (1) the PPHS, which included information provided by a relative or carer, (2) the SCAN and (3) clinical case notes. Data on drug use from these sources were collated retrospectively using an *ad hoc* secondary data collection schedule, which collated data on prevalence and type of substance use from all three sources. Where discrepancies between schedules were present, a hierarchical system was adopted: the information on drug use collected using the SCAN was deemed the most reliable, followed by the PPHS, and finally, clinical case notes. For the purposes of this study, a dichotomous variable for lifetime cannabis use or no use was created, where 'use' signified any use at all of cannabis before the first contact with mental health services. 'No use' represented those individuals who had not used cannabis before their first contact with mental health services. The variable 'Other drug use' was a dichotomous variable where 'no use' included those individuals who had never used an illegal substance (other than cannabis) in the time before their first contact with mental health services for psychosis.

2.1. Statistical analysis

Independent samples *t*-tests, χ^2 and Mann–Whitney *U* analysis were performed where appropriate to compare those for whom data on illegal drug use was available and for those for whom it was not. A Kaplan–Meier survival curve for age of onset of psychotic symptoms according to gender and cannabis use status was plotted. Cox proportional hazards regression was used to compare the effects of cannabis use and gender on age of onset of psychotic symptoms and expressed as hazard ratios. The proportional hazards assumption was checked using the scaled Schoenfeld residuals and no violation was detected. The Cox proportional hazards regression models were evaluated according to Akaike's information criteria (AIC) to determine the model that best fitted the data. AIC is a method of model selection, based on information theory, that compares the trade-off between the simplicity and goodness of fit of candidate models, aiming to find the model(s) with the best predictive validity in a future dataset. (Akaike, 1974). A smaller AIC indicates a better model. All analyses were conducted using Stata version 11 (StataCorp, 2009) and the alpha level was set at 0.05 (two-tailed).

3. Results

Of the 511 participants included in the original AESOP study, 211 participants had an onset of symptoms before the age of 45 and a diagnosis of schizophrenia or schizoaffective disorder. Sixty-eight of these lacked data on cannabis use, leaving a sample of 143 for subsequent analyses. Key demographic data were compared for those with and without available information on cannabis use (Table 1), and there were no statistically significant differences between the two groups ($p > 0.05$). Eighty five of the 143 participants included in the sample (59%) had a history of cannabis use in their lifetime.

Cannabis users were younger at onset of psychotic symptoms and at first contact with mental health services compared to non-users. A greater proportion of males had a history of cannabis use compared to females and a higher proportion of cannabis users had a history of other illegal drug use than those with no history of cannabis use. There was no difference between cannabis users and non-cannabis users for ethnicity, education level, employment status, DUP or Mode of Onset.

Fig. 1 presents the Kaplan–Meier survival curve for the cumulative probability, by age, of the onset symptoms in males and females according to lifetime cannabis use.

The mean age of psychotic symptom onset for males with no lifetime cannabis use was 27.07 (standard deviation (S.D.)=7.23) compared to a mean age of 30.76 (S.D.=8.15) for females. A similar mean age of psychotic symptom onset was found for males (mean=25.52, S.D.=6.62) and females (mean=26.03, S.D.=5.56) who had a history of cannabis use.

Cox proportional hazards regression analysis was used to investigate the contribution of gender and cannabis use to age at symptom onset (Table 2). Male gender significantly contributed to age at symptom onset as did cannabis use. When age and gender were entered into a model together, cannabis use remained significant with a reduction in hazard ratio but male gender was no longer significant. The interaction between gender and cannabis use was significant.

A large number of cannabis users (72.9%) also used other illegal drugs, therefore this variable was entered into a model, but this had little effect on the hazard ratios for the interaction for gender and cannabis use status.

AIC was calculated to determine the best model (Table 3), the results of this analysis indicate that the model containing the interaction between cannabis use and gender only is the best with 28.7% probability. Adding information on other illegal drug use does not improve the fit. The model including gender alone fits the data much more poorly.

4. Discussion

4.1. Summary of findings

The use of cannabis is associated with an earlier age of onset of schizophrenia. There is a significant interaction between gender and cannabis use whereby the gender difference in age of onset is diminished in cannabis users.

4.2. Association of cannabis use with earlier age of onset

The finding of an earlier age of onset in cannabis users is consistent with the results of a recent meta-analysis (Large et al., 2011). There are a number of potential explanations for an association between cannabis use and age of onset of schizophrenia (Large et al., 2011; Veen et al., 2004). A first possible explanation is of confounding by age; that cannabis use has no impact on age of onset of schizophrenia and the association seen is due to substance use being more common in younger, compared to older, individuals. However, the small age range of this population makes this explanation unlikely – furthermore, the finding that cannabis