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Trends in cannabis use prior to first presentation with schizophrenia, in South-East London between 1965 and 1999

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ABSTRACT

Background. There is evidence that cannabis use might be relevant to the aetiology of schizophrenia. We aimed to measure any change in cannabis use over time in those first presenting with schizophrenia in South-East London from 1965 to 1999, and compare this with change in use in those presenting with non-psychotic psychiatric disorders.

Method. The rate of cannabis use in the year prior to first ever presentation was measured over seven time periods. Logistic regression modelling was used to determine (*a*) whether cannabis use changed over time, after controlling for age, sex and ethnicity, and (*b*) whether there was an interaction between diagnosis and time.

Results. Cannabis use increased over time in both the schizophrenia group [odds ratio per time period (OR) 2·03, 95% confidence interval (CI) 1·74–2·38, $p<0·0001$] and the non-psychotic disorders group (OR 1·24, 95% CI 1·05–1·47, $p=0·012$), after controlling for age, sex and ethnicity. However, the effect of time was significantly greater in the schizophrenia group than in the non-schizophrenia group ($\chi^2=17$, $p<0·0001$).

Conclusion. Cannabis use in the year prior to presentation with schizophrenia increased markedly between 1965 and 1999, and disproportionately so compared to increase in cannabis use in other psychiatric disorders.

INTRODUCTION

There is considerable interest in the role of cannabis as an aetiological factor in the development of schizophrenia and other psychoses (Arseneault *et al*. 2004; Smit *et al*. 2004). Several cross-sectional studies have shown high rates of cannabis use among people with psychosis in both patient populations (Grech *et al*. 2005) and general population surveys (Johns *et al*. 2004). The strongest evidence for causality comes from cohort studies that have shown that cannabis use is associated with increased odds (2 to 3) of subsequently developing schizophrenia (Andreasson *et al*. 1987; Arseneault *et al*. 2002; Van Os *et al*. 2002; Zammit *et al*. 2002; Fergusson *et al*. 2005; Henquet *et al*. 2005*a*). We previously demonstrated a considerable increase in the incidence of schizophrenia in South-East London over the past 35 years (Boydell *et al*. 2003). The rise was most notable in people under 35 years, and occurred mostly in the 1980s and 1990s. We wanted to determine whether part of this increase might be related to cannabis use. We therefore tested the hypothesis that the rate of cannabis use had increased among people presenting with schizophrenia. To control for period effects, we also examined whether any increase found was greater than any increase noted in people

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presenting to the same services with non-psychotic disorders.

METHOD

This study was carried out using cases of schizophrenia from the Camberwell Psychosis Database, which has been compiled over the past four decades (Castle *et al.* 1991; Allardyce *et al.* 2000, 2001; Boydell *et al.* 2001, 2003), and an equivalent comparison group of cases with other (non-psychotic) psychiatric disorders.

Sample

We collected clinical and demographic data on all people aged over 16 years from the geographically defined area of Camberwell in South London, who presented to psychiatric services with any possible psychotic illness between 1965 and 1999. This 35-year period was broken down into seven 5-year periods (1965/69 = 1, 1970/74 = 2, 1975/79 = 3, 1980/84 = 4, 1985/89 = 5, 1990/94 = 6, 1995/99 = 7). Cases were initially identified using the Camberwell Case Register (Wing & Hailey, 1972) and then psychiatric hospital computer records (from 1984) and searching all case records from the area to identify those not admitted or missed from the register or computer record. The methodology is more fully described in previous publications (Castle *et al.* 1998; Allardyce *et al.* 2001; Boydell *et al.* 2001, 2003).

Diagnosis, and measurement of cannabis use

All patients' records were checked to ensure that they were true incident cases (i.e. had not presented with, or had prior psychiatric treatment for, psychosis), and then were rated using the Operational Criteria (OPCRIT) checklist (for further details including evidence of inter-rater reliability, see Castle *et al.* 1991, 1998; Van Os *et al.* 1996; Allardyce *et al.* 2001; Boydell *et al.* 2001, 2003). The OPCRIT checklist includes clear definitions of most symptoms and signs and their duration seen in mood disorders and psychosis, which are then used to generate diagnoses using a computer program (further description of OPCRIT including a discussion of reliability and validity can be found in McGuffin *et al.* 1991). We used Research Diagnostic Criteria (RDC; Spitzer *et al.* 1978) as these criteria have been incorporated in the OPCRIT system from the beginning, thus avoiding difficulties with the changes between different versions of DSM and ICD. Within the RDC we chose the narrow definition of schizophrenia (see Appendix for description; McGuffin *et al.* 1984) as this enabled us to avoid including drug-induced psychoses (brief psychotic reactions to intoxication). Cannabis use in the year prior to presentation was rated from the case-notes as either used, not used, or not known. This was based on self-report and urine drug screening so that if either was positive for cannabis the item was rated as 'used'. The case-notes all came from the Maudsley Hospital and its associated hospitals, and follow a standardized format including a section on drug use. This item was rated by J.B. and N.K. yielding inter-rater reliability, expressed as a κ statistic of 0·81, based on a random sample of 50.

The comparison group

A comparison group from the same area, presenting to the same services, was identified by randomly selecting case records, in such a way that each set of records had an equal chance of being selected, of people aged 16 years and over who first presented in each of the seven time periods but received non-psychotic psychiatric diagnoses. People with organic disorders (such as dementia), other psychoses (such as bipolar disorder) or a primary diagnosis of substance abuse were excluded. The diagnosis was the clinical diagnosis and included a range of diagnoses such as anxiety, depressive and personality disorders. Cannabis use was rated in the same way as for the schizophrenia cases by the same researchers.

Statistical analyses

Cannabis use was modelled by logistic regression analysis using STATA version 8 (Stata Corporation, 2002), with diagnostic status and time period as the main explanatory variables. Confounders included in the models were age at onset (in 10-year age bands), sex and ethnicity. (For a description of how ethnicity was identified and classified, see Boydell *et al.* 2001.) For this analysis, it was necessary to combine Black African, Black Other and African Caribbean people as one group, White British and White Other as another. Explanatory variables were tested using the likelihood ratio test to

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Table 1. *Number and percentage of cases using cannabis in the year prior to onset by diagnostic group and time*

	Schizophrenia			Other diagnoses		
Time period	No cannabis use, *n* (%)	Cannabis use, *n* (%)	Missing, *n* (%)	No cannabis use, *n* (%)	Cannabis use, *n* (%)	Missing, *n* (%)
1 (1965–1969)	58 (95)	3 (5)	0 (0)	53 (88)	5 (8)	2 (3)
2 (1970–1974)	64 (95)	3 (5)	0 (0)	43 (86)	3 (6)	4 (8)
3 (1975–1979)	69 (96)	3 (4)	0 (0)	50 (83)	7 (12)	3 (5)
4 (1980–1984)	63 (85)	8 (11)	3 (4)	53 (88)	6 (10)	1 (2)
5 (1985–1989)	61 (69)	26 (29)	2 (2)	53 (88)	6 (10)	1 (2)
6 (1990–1994)	85 (67)	37 (29)	5 (4)	51 (85)	9 (15)	0 (0)
7 (1995–1999)	48 (40)	59 (50)	12 (10)	47 (78)	13 (22)	0 (0)
Total	448 (74)	139 (23)	22 (4)	350 (85)	49 (12)	11 (3)

'Missing' refers to information on cannabis use, these cases were not included in the analysis.

determine whether they improved the model. Preliminary analysis suggested a fivefold increase in cannabis use between the first and the last two time periods among the schizophrenia group. To assess whether any increase in cannabis use was different for the two diagnostic groups, a time × diagnosis interaction was fitted, testing the following simplified model: cannabis use = time + diagnostic group + (time × diagnosis), adjusting for the effects of age, gender and ethnicity.

RESULTS

According to the OPCRIT computer program, a total of 609 cases met the RDC for narrowly defined schizophrenia. Twenty-two cases had missing information on cannabis use and these were not included in the analysis. There were 410 cases in the non-psychotic comparison group. The mean age for the schizophrenia group was 35·5 (S.D. = 18·5) years, and for the control group 36·1 (S.D. = 14) years. The schizophrenia group was 54% male and 46% female, and the control group was 48% male and 52% female. The numbers in each time period and the percentage who had used cannabis in the year prior to presentation are shown in Table 1. Logistic regression modelling revealed that cannabis use increased over time in both the schizophrenia group [odds ratio per time period (OR) 2·03, 95% confidence interval (CI) 1·74–2·38 $p < 0·0001$] and the non-psychotic disorders group (OR 1·24, 95% CI 1·05–1·47, $p = 0·012$) after controlling for age, sex and ethnicity. There was a highly statistically significant interaction between diagnosis (of schizophrenia) and time, indicating that the effect of time was significantly greater in the schizophrenia than in the non-psychotic disorders group ($\chi^2 = 17$, $p < 0·0001$).

Table 2. *Change in cannabis use over time in schizophrenia and other disorders: odds ratios (ORs) and 95% confidence intervals (CIs) from logistic regression*

Explanatory variable	OR (95% CI)	*p*
Diagnostic group at baseline (i.e. earliest time period)	0·13 (0·04–0·46)	0·001
Time	1·23 (1·04–1·45)	0·014
Diagnostic group × time (i.e. interaction term)	1·62 (1·29–2·04)	0·0001
Age at onset	0·94 (0·93–0·96)	0·0001
Sex (female = 1, male = 0)	0·34 (0·23–0·5)	0·019

Ethnicity did not improve the model and was therefore not included (see text for further details).

In the full model including the time × diagnosis interaction and the confounders, the odds of cannabis use were lower in older people (OR 0·94, 95% CI 0·93–0·96, $p < 0·0001$ with increasing age) and in women (OR 0·34, 95% CI 0·23–0·5, $p < 0·0001$ for women). There was no significant effect of ethnicity on cannabis use after controlling for age, sex, diagnosis, time and the diagnosis × time interaction (Table 2).

DISCUSSION

We found that cannabis use in the year prior to presentation to the psychiatric services in South-East London increased between 1965 and 1999 in both patients with schizophrenia and those

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with non-psychotic disorders. However, the increase in the former group was much greater than in the latter even after we controlled for age, sex and ethnicity. These findings are compatible with growing evidence that cannabis use is a contributory cause of schizophrenia, as evidenced by recent reviews and meta-analyses of epidemiological data (Arseneault *et al*. 2004; Henquet *et al*. 2005*b*; Semple *et al*. 2005).

The use of another patient group as a control group has limitations, notably whether aspects of their illness might have biased their exposure. For example, it is possible that non-psychotic psychiatric patients might have used less cannabis than the general population and might not have increased their use over time, thus accounting for the divergence of the rates of use between psychotic and non-psychotic cases. This seems unlikely as several studies have reported an association between cannabis use and anxiety and depression (Degenhardt *et al*. 2004). As far as we can ascertain, no studies of cannabis use over time (spanning 1965–1999) have been carried out in South-East London or a comparable area. Four national surveys (British Crime Survey, 1992, 1994, 1996 and 1998) that asked individuals about their cannabis use in the past year are relevant to time periods 6 and 7 in this study. The data are not directly comparable because of the difference in geographical coverage, and furthermore, the 1992 survey is not considered comparable with the later ones as the methodology changed. Nevertheless, these surveys found that rates of cannabis use in the past year in the general population (age 16 to 59) increased from 5% in 1992 to 9% in 1998 although these rates were probably higher in urban areas, consistent with the findings in our non-psychotic group. We were only able to classify cannabis use as present or absent as data regarding age at first use or intensity of use was not recorded in a consistent or standardized way.

The possible impact of increasing population use of cannabis on the incidence of psychosis is an important consideration. One study addressed this indirectly and suggested there would be no impact on incidence (Degenhardt *et al*. 2003). However, this study included the premise that incidence had not increased and did not measure incidence of psychosis in the area studied, and therefore could not reach a conclusion that incidence would increase. In the past century there were a number of suggestions that incidence of schizophrenia was decreasing, although these studies were mostly carried out before the increase in cannabis use and in times of great service change (Munk-Jorgensen, 1995). It may also be (although this is speculative) that 'use' in our study is a proxy for early use and that it is early use that leads to increasing incidence.

One possible explanation for our findings is that of reverse causality, that is those developing schizophrenia or its prodromal state are more likely to use cannabis, perhaps to relieve their symptoms. However, this possibility has been much researched in studies examining a possible aetiological role for cannabis in psychosis and has generally been dismissed as unlikely. For example, Fergusson *et al*. (2005) used structural equation modelling in a cohort study to examine whether having psychotic symptoms increased cannabis consumption. They concluded that the effect of psychotic symptoms was negative, and 'if anything the development of these symptoms may have inhibited rather than encouraged cannabis use'.

Other methodological issues need to be addressed. The categorization of cannabis use was based on responses to routine clinical questioning and routine urine drug screening recorded in case-notes. This is therefore vulnerable to information bias. If the doctors were more persistent when questioning a psychotic person and more likely to request a urine drug screen then they would have been more likely to identify cannabis use. Recall bias, whereby people with psychosis or in the later time periods might be more likely to remember or admit to cannabis use, is also possible. These possible biases are, however, unlikely to account for the scale of the fivefold increase over time that we found in the schizophrenia group or the divergence between the groups over time.

Selection bias is unlikely to have had an effect in this study as all psychiatric contacts from a defined area were included and it is thought that almost everyone with schizophrenia in the UK comes into contact with psychiatric services (Prince & Phelan, 1994). Diagnostic error with drug-induced psychosis being misdiagnosed as schizophrenia is also unlikely as the use of a narrow definition of schizophrenia should have excluded cases who only had a brief psychotic reaction to cannabis.

Several potential confounders could have accounted for our findings but we were able to control for the most important, including age, sex and ethnicity. Other possible confounders would be any factors that have changed over time and are associated with both cannabis use and schizophrenia, for example other drug use/urbanicity; however, these are unlikely to have increased to the same extent. Social change might also be associated with increased cannabis use and serious mental illness.

This study did not have an experimental design and therefore cannot prove causality but it does add to the evidence. It is also limited to one geographical area. The strength of the study is that it used a large, and possibly unique, comprehensive dataset of all cases of a relatively rare disorder to describe changes over time in a defined area and to identify a suitable comparison group.

Summary of findings

We have demonstrated a large and disproportionate increase in cannabis use in the year prior to first presentation with narrowly defined schizophrenia, in South-East London between the years 1965 and 1999. We found a smaller increase in people from the same area presenting with non-psychotic psychiatric disorders. The differential increase remained after adjusting for age at onset, sex and ethnicity.

CONCLUSION

Our findings are compatible with evidence from other studies that cannabis use might have an aetiological role in the development of schizophrenia, and it is plausible that its increased consumption or earlier consumption might account for some of the increase in the incidence of schizophrenia that we reported previously in South-East London. (Boydell *et al*. 2003).

APPENDIX

OPCRIT checklist items used to establish a diagnosis of research diagnostic criteria using a 'narrow definition of schizophrenia' (McGuffin *et al*. 1984)

- Illness duration of at least 2 weeks.
- Affective symptoms must not be prominent.
- Two of catatonia (speech incoherent, formal thought disorder), (well-organized delusional system, grandiose delusions, delusions of influence), (bizarre delusions, widespread delusions, delusions of passivity), delusions with hallucinations lasting a week or more (thought insertion, thought withdrawal, thought broadcast), abusive/accusatory/persecutory voices, other non-affective auditory hallucinations where one or more of the items in parentheses scores 1.

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DECLARATION OF INTEREST

None.

REFERENCES

Allardyce, J., Boydell, J., van Os, J., Morrison, G., Castle, D. & Murray, R. M. (2001). A comparison of the incidence of schizophrenia in rural Dumfries and Galloway and urban Camberwell. *British Journal of Psychiatry* **179**, 335–339.

Allardyce, J., Morrison, G., Van Os, J., Kelly, J., Murray, R. M. & McCreadie, R. G. (2000). Schizophrenia is not disappearing in southwest Scotland. *British Journal of Psychiatry* **177**, 38–41.

Andreasson, S., Allebeck, P., Engstrom, A. & Rydberg, U. (1987). Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. *Lancet* **2**, 1483–1486.

Arseneault, L., Cannon, M., Poulton, R., Murray, R., Caspi, A. & Moffitt, T. E. (2002). Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *British Medical Journal* **325**, 1212–1213.

Arseneault, L., Cannon, M., Witton, J. & Murray, R. M. (2004). Causal association between cannabis and psychosis: examination of the evidence. *British Journal of Psychiatry* **184**, 110–117.

Boydell, J., van Os, J., Lambri, M., Castle, D., Allardyce, J., McCreadie, R. G. & Murray, R. M. (2003). Doubling in incidence of schizophrenia in south-east London between 1965 and 1997. *British Journal of Psychiatry* **182**, 45–49.

Boydell, J., van Os, J., McKenzie, K., Allardyce, J., Goel, R., McCreadie, R. G. & Murray, R. M. (2001). Incidence of schizophrenia in ethnic minorities in London: ecological study into interactions with environment. *British Medical Journal* **323**, 1336–1338.

Castle, D., Wessely, S., Der, G. & Murray, R. M. (1991). The incidence of operationally defined schizophrenia in Camberwell, 1965–1984. *British Journal of Psychiatry* **171**, 140–144.

Castle, D., Wessely, S., van Os, J. & Murray, R. M. (1998). *Psychosis in the Inner City: The Camberwell First Episode Study*. Maudsley Monographs, 40. Psychology Press: Hove.

Degenhardt, L., Hall, W. & Lynskey, M. (2003). Testing hypotheses about the relationship between cannabis use and psychosis. *Drug and Alcohol Dependence* **71**, 37–48.

Degenhardt, L., Hall, W., Lynskey, M., Coffey, C. & Patton, G. (2004). The association between cannabis use and depression: a review of the evidence. In *Marijuana and Madness* (ed. D. Castle

and R. Murray), pp. 54–75. Cambridge University Press: Cambridge.

Fergusson, D. M., Horwood, L. J. & Ridder, E. M. (2005). Tests of causal linkages between cannabis use and psychotic symptoms. *Addiction* **100**, 354–366.

Grech, A., van Os, J., Jones, P. B., Lewis, S. W. & Murray, R. M. (2005). Cannabis use and outcome of recent psychosis. *European Psychiatry* **20**, 349–353.

Henquet, C., Krabbendam, L., Spauwen, J., Kaplan, C., Lieb, R., Wittchen, H. U. & van Os, J. (2005*a*). Prospective cohort study of cannabis use, predisposition for psychosis and psychotic symptoms in young people. *British Medical Journal* **330**, 11.

Henquet, C., Murray, R., Linszen, D. & van Os, J. (2005*b*). The environment and schizophrenia: the role of cannabis use. *Schizophrenia Bulletin* **31**, 608–612.

Johns, L. C., Cannon, M., Singleton, N., Murray, R. M., Farrell, M., Brugha, T., Bebbington, P., Jenkins, R. & Meltzer, H. (2004). Prevalence and correlates of self-reported psychotic symptoms in the British population. *British Journal of Psychiatry* **185**, 298–305.

McGuffin, P., Farmer, A., Gottesman, I., Murray, R. M. & Reveley, A. (1984). Twin concordance for operationally defined schizophrenia. *Archives of General Psychiatry* **41**, 541–545.

McGuffin, P., Farmer, A. & Harvey, I. (1991). A polydiagnostic application of operational criteria in studies of psychotic illness. *Archives of General Psychiatry* **48**, 764–770.

Munk-Jorgensen, P. (1995). Decreasing rates of incident schizophrenia cases in psychiatric service: a review of the literature. *European Psychiatry* **10**, 129–141.

Prince, M. & Phelan, M. (1994). Invisible schizophrenia: a postal survey of the incidence and management of new cases of schizophrenia in primary care. *Journal of Mental Health* **3**, 91–98.

Semple, D. M., McIntosh, A. M. & Lawrie, S. M. (2005). Cannabis as a risk factor for psychosis: systematic review. *Journal of Psychopharmacology* **19**, 187–194.

Smit, F., Bolier, L. & Cuijpers, P. (2004). Cannabis use and the risk of later schizophrenia: a review. *Addiction* **99**, 425–430.

Spitzer, R. L., Endicott, J. & Robins, E. (1978). Research Diagnostic Criteria: rationale and reliability. *Archives of General Psychiatry* **35**, 773–782.

Stata Corporation (2002). *STATA Statistical Software: Release 8.0*. Stata Corporation, College Station: TX, USA.

Van Os, J., Bak, M., Hanssen, M., Bijl, R. V., de Graaf, R. & Verdoux, H. (2002). Cannabis use and psychosis: a longitudinal population-based study. *American Journal of Epidemiology* **156**, 319–327.

Van Os, J., Castle, D. J., Takei, N., Der, G. & Murray, R. M. (1996). Psychotic illness in ethnic minorities: clarification from the 1991 census. *Psychological Medicine* **26**, 203–208.

Wing, J. K. & Hailey, A. M. (1972). *Evaluating a Community Psychiatric Service: The Camberwell Register 1964–1971*. Oxford University Press: London.

Zammit, S., Allebeck, P., Andreasson, S., Lundberg, I. & Lewis, G. (2002). Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. *British Medical Journal* **325**, 1199.