14TLP0454_Di Forti
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THELANCETPSYCH-D-14-00454R1
S2215-0366(14)00117-5
Embargo: February 18, 2015—00:01 (GMT)
NIHR funding / Gold OA: CC BY

Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study

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Summary

Background The risk of individuals having adverse effects from drug use (eg, alcohol) generally depends on the frequency of use and potency of the drug used. We aimed to investigate how frequent use of skunk-like (high-potency) cannabis in south London affected the association between cannabis and psychotic disorders.

Methods We applied adjusted logistic regression models to data from patients aged 18–65 years presenting to South London and Maudsley NHS Foundation Trust with first-episode psychosis and population controls recruited from the same area of south London (UK) to estimate the effect of the frequency of use, and type of cannabis used on the risk of psychotic disorders. We then calculated the proportion of new cases of psychosis attributable to different types of cannabis use in south London.

Findings Between May 1, 2005, and May 31, 2011, we obtained data from 410 patients with first-episode psychosis and 370 population controls. The risk of individuals having a psychotic disorder showed a roughly three-times increase in users of skunk-like cannabis compared with those who never used cannabis (adjusted odds ratio [OR] 2·92, 95% CI 1·52–3·45, p=0·001). Use of skunk-like cannabis every day conferred the highest risk of psychotic disorders compared with no use of cannabis (adjusted OR 5·4, 95% CI 2·81–11·31, p=0·002). The population attributable fraction of first-episode psychosis for skunk use for our geographical area was 24% (95% CI 17–31), possibly because of the high prevalence of use of high-potency cannabis (218 [53%] of 410 patients) in our study.

Interpretation The ready availability of high potency cannabis in south London might have resulted in a greater proportion of first onset psychosis cases being attributed to cannabis use than in previous studies.

Funding UK National Institute of Health Research (NIHR) Specialist Biomedical Research Centre for Mental Health, SLaM and the Institute of Psychiatry at King's College London, Psychiatry Research Trust, Maudsley Charity Research Fund, and th European Community's Seventh Framework Program grant (agreement No. HEALTH-F2-2009-241909 [Project EU-GEI]).

Introduction

Cannabis is the most popular illicit drug in the world. Uruguay was the first country to legalise its use and several US states have done so or are in the process of doing similar.[1] Therefore, any harm caused by cannabis use should be quantified. Prospective epidemiological studies have consistently reported that use of cannabis increases the risk of schizophrenia-like psychosis.[2,3] In the UK, the investigators of the 2012 Schizophrenia Commission[4] concluded that cannabis use is the most preventable risk factor for psychosis, and research that aims to improve estimation of the drug's contribution to illness development should be pursued.

The aspects of exposure to cannabis (eg, age at first use, frequency of use, duration of use) that confer the greatest effect on risk of psychosis are unclear. Such information would be valuable for public education and to estimate the proportion of psychosis cases that could be prevented if harmful patterns of cannabis use were removed from the population. The few studies[5,6] that have tried to estimate the effect of cannabis use on the number of new cases of psychosis in specific populations have been limited by the scarcity of accurate information on patterns of cannabis use.

The risk of adverse effects for mental health and cognition posed by cannabis use has been suggested to depend on the potency of the type of cannabis used.[7] For example, in a previous study[8] of part of the population reported here, we noted that skunk-like types of cannabis, which contain very high concentrations of Δ-9-tetrahydrocannabinol (THC), seemed to have a greater psychotogenic effect than did hash (resin), which is known to contain much less THC.

We analysed detailed data for history of cannabis use, aiming to: compare the patterns and types of cannabis used between patients with first-episode psychosis and a

Lancet Psychiatry 2015
Published Online
February 18, 2015
http://dx.doi.org/10.1016/S2215-0366(14)00117-5
See Online/Comment
http://dx.doi.org/10.1016/S2215-0366(14)00130-8

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population control sample; use the data for pattern of cannabis use to develop a cannabis exposure measure that accurately estimates the risk of psychotic disorders; and calculate the proportion of cases of psychosis in our study area attributable to use of cannabis, particularly high-potency cannabis, if we assumed causality.

Methods

Study design and participants

As part of the GAP study,[8] we did a case-control study at the inpatient units of the South London and Maudsley (SLaM) NHS Foundation Trust. We approached all patients aged 18–65 years who presented with first-episode psychosis. We invited patients to participate if they met the International Classification of Diseases 10 criteria for a diagnosis of non-affective (F20–F29) or affective (F30–F33) psychosis, validated by administration of the Schedules for Clinical Assessment in Neuropsychiatry (SCAN).[9] We excluded individuals who met the criteria for organic psychosis (F09). If patients were too unwell to cooperate, we re-contacted them after the start of treatment.

We recruited controls using internet and newspaper advertisements and by distributing leaflets at train stations, shops, and job centres. None of the advertising material mentioned cannabis or illicit drug use. Volunteers were administered the Psychosis Screening Questionnaire[10] and were excluded if they met the criteria for a psychotic disorder or if they reported a previous diagnosis of psychotic illness. This study is part of the GAP study, which was granted ethical approval by SLaM and Institute of Psychiatry Local Research Ethics Committee. All case and control individuals included in the study gave written informed consent.

Procedures

We obtained sociodemographic data using the Medical Research Council Schedule.[11] From March, 2006, we took a more detailed history of cannabis use by adding the Cannabis Experience Questionnaire modified version (CEQ_{mv}) to the assessment.[8,12] From the CEQ_{mv}, we derived information on history of use of tobacco, alcohol, other recreational drugs, and detailed information on cannabis use (age at first use, duration of use, frequency of use, type used).

Measures of cannabis use relevant to the analysis were: lifetime history of cannabis use—ie, had the individual ever used cannabis at any point in their life (no scores 0, yes scores 1); lifetime frequency of cannabis use—ie, the frequency that characterised the individual's most consistent pattern of use (none scores 0, less than once per week every week scores 1, at weekends scores 2, every day scores 3); and type of cannabis used—ie, the type most used by the subject (none scores 0, low potency [hash-type] scores 1, high potency [skunk-type] scores 2). This variable was grouped in accordance with the characteristics of the cannabis samples seized by the Metropolitan Police in London, as reported by Potter and colleagues[13] and the Home Office study (appendix).[14] Finally, we used a seven-item composite cannabis exposure measure derived from the lifetime frequency of use and the most used type (none scores 0, hash less than once per week every week scores 1, hash at weekends scores 2, hash every day scores 3, skunk less than once per week scores 4, skunk at weekends scores 5, skunk every day scores 6) to investigate which patterns of use conferred the greatest risk.

See Online for appendix

Statistical analysis

We analysed data using Stata 13. We used χ^2 tests and *t* tests (or Mann-Whitney U tests) to test for associations between potential confounding variables and between presence of psychotic disorder and exposure to cannabis use. We also used these tests to establish whether missing data for the cannabis use exposure were associated with case-control status and therefore likely to bias the results.

We used logistic regression to analyse whether individual indicators of cannabis use (lifetime use, age at first use, duration and frequency of use, and most used type of cannabis) improved estimation of the likelihood of psychotic disorders (ie, case status), in comparisons of cannabis users with non-users.

We used the *punafcc* command in Stata 13 to estimate the population attributable fraction (PAF), with confidence intervals, for each cannabis use variable. The PAF measures the population effect of an exposure by providing an estimate of the proportion of disorder that would be prevented if the exposure were removed. However, causality does not have to be proven before the PAF can be estimated, and this causation is not usually established when PAFs are estimated (indeed no single study could ever prove causation). Because the same proportion of disorder attributable to a specific risk factor can also be attributable to other factors with which the specific risk factor might interact, PAFs for multiple risk factors can add up to more than 100%. Furthermore, the PAF depends on both the prevalence of exposure (ie, measures of cannabis use) in cases and the odds ratio (OR) for the exposure, such that a risk factor with a modest OR can have a major population effect if the factor is common.

Role of the funding source

All funders contributed to data collection by providing the salaries of the research workers collecting the data. The funders of the study had no role in study design, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between May 1, 2005, and May 31, 2011, we approached 606 patients with first-episode psychosis. Of these 606 patients, 145 (24%) refused to participate. Thus, we recruited 461 patients with first-episode psychosis. Patients who refused to participate were more likely to be men ($p<0\cdot004$) and of Black Caribbean and Black African ethnic

	First-episode psychosis group (n=410)	Control group (n=370)	p value
Age, years	27·1 (8·7)	30·0 (9·0)	0·0001
Gender	..	..	0·004
Male	271 (66%)	209 (56%)	..
Female	139 (34%)	161 (44%)	..
Ethnic origin	..	..	0·0001
White	132 (32%)	212 (57%)	..
Black Caribbean	136 (33%)	73 (20%)	..
Black African	98 (24%)	38 (10%)	..
Asian/other	44 (11%)	47 (13%)	..
Education	..	..	0·0003
No qualification	60 (15%)	8 (2%)	..
GCSEs	116 (28%)	31 (8%)	..
A levels or vocational training	153 (37%)	151 (41%)	..
University	81 (20%)	180 (49%)	..
Ever employed	..	..	0·001
Yes	361 (88%)	353 (95%)	..
No	46 (11%)	15 (4%)	..
No details	3 (1%)	2 (1%)	..

Data are mean (SD) or n (%) unless stated otherwise.

Table 1: **Population sociodemographics**

	First-episode psychosis group (n=410)	Control group (n=370)	p value
Total population			
Lifetime history of cannabis use	..	..	0·277
Yes	275 (67%)	232 (63%)	..
No (never used)	135 (33%)	138 (37%)	..
Frequency of use	..	..	<0·0001
Less than once per week	68 (17%)	128 (35%)	..
At weekends	84 (20%)	63 (17%)	..
Every day	123 (30%)	41 (11%)	..
Most used type of cannabis	..	..	<0·0001
Never used	135 (33%)	138 (37%)	..
Hash-like	57 (14%)	162 (44%)	..
Skunk-like	218 (53%)	70 (19%)	..
Cannabis users			
Duration of use (years)	9·7 (7·4)	9·1 (7·8)	0·635
No details	3	1	..
Age at first cannabis use (years)	16·1 (4·2)	16·6 (3·2)	0·146
No details	3	1	..
Age at first use ≤15 years	..	..	0·028
No	172 (63%)	178 (77%)	..
Yes	100 (36%)	53 (23%)	..
No details	3	1	..

Data are n (%) or mean (SD) unless stated otherwise.

Table 2: **Cannabis use**

origin (p=0·001) than were those who consented. Therefore, in all the analyses, we tested for the potential confounding effects of ethnic origin and gender. During the same period and from the geographical area served by the clinical units, we recruited 389 control individuals, aged 18–65 years, who were similar to the local population in terms of ethnic origin, education, and employment status (table 1). The later addition of CEQ_{mv} meant that there were data missing on detailed patterns of cannabis use for those participants recruited early in the project. The data we present here are therefore based on 410 (89%) of 461 patients with first-episode psychosis and 370 (95%) of 389 controls for whom we had data for cannabis use.

The patients with first-episode psychosis consisted of more men and were younger than the control group (table 1). As noted previously,[15] patients with first-episode psychosis were also more likely to be of Black ethnic origin (Caribbean or African) compared with controls, and less likely to have completed a high level of education than were controls (table 1).

A larger proportion of patients with first-episode psychosis (184 [45%] of 410 individuals) reported having smoked 100 tobacco cigarettes or more than did controls (60 [16%] of 370 individuals; p<0·0001), but the groups did not differ in lifetime history of other substance use (p=0·615), or alcohol units consumed per week (p=0·083). Patients with first-episode psychosis were no more likely than were controls to report a lifetime history of ever having used cannabis, but were more likely to use cannabis every day and to mostly use high-potency (skunk-like) cannabis (table 2). A small proportion of cannabis users (3 [0·6%] of 507 individuals) reported having used cannabis more than four days a week and they were included in the every day category.

For more on **demographic composition of the local population** see www.statistics.gov.uk/census

Among cannabis users, the mean duration of use did not differ between patients with first-episode psychosis and controls (table 2). On average, both groups started using cannabis in their mid-teens, although distribution of the age at first cannabis use seemed to be skewed (mean 16·1 years, SD 4·2, median 16 years in the patients with first-episode psychosis *vs* mean 16·6 years, SD 3·2, median 17 years in the control group; Z=2·88; p=0·146). Patients with first-episode psychosis were more likely to start using cannabis at age 15 years or younger than were controls.

When we combined data on frequency of cannabis use and most used type into a single variable, the composite cannabis exposure measure, controls were more likely to be occasional users of low-potency cannabis (hash), and patients with first-episode psychosis were more likely to be daily users of high-potency cannabis (skunk; figure 1; p<0·0001).

A logistic regression, adjusted for age, gender, ethnic origin, number of cigarettes smoked, alcohol units and lifetime use of other illicit drugs, education, and employment history, showed that individuals who had ever used cannabis were not at increased risk of psychotic disorder compared with those who had never used

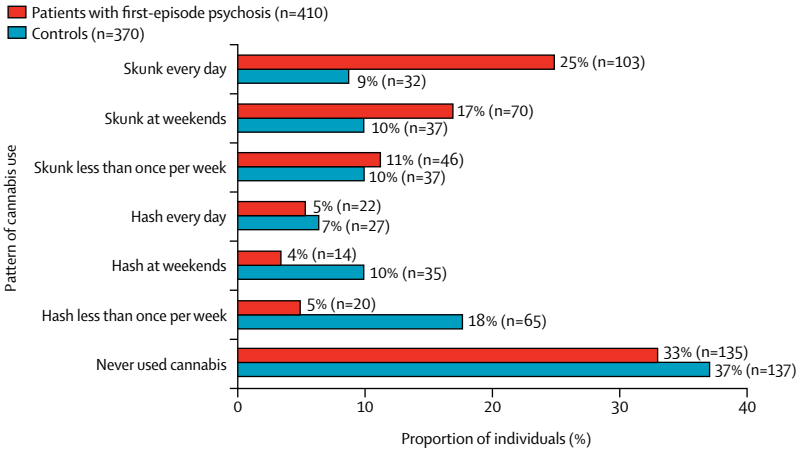

Figure 1: **Patterns of cannabis use between patients with first-episode psychosis and population controls**

	Odds ratio* (95% CI)	p value
Age at first use, years		
Never used	1	..
≥15 years	0·68 (0·34–1·37)	0·292
<15 years	1·55 (1·00–1·39)	0·048
Frequency of use		
Never used	1	..
Less than once per week	0·58 (0·25–1·32)	0·198
Weekends	1·04 (0·41–1·62)	0·929
Every day	3·04 (1·91–7·76)	0·020
Most used type		
Never used	1	..
Hash-like	0·83 (0·52–1·77)	0·903
Skunk-like	2·91 (1·52–3·60)	0·001

*Adjusted for age, gender, ethnic origin, number of cigarettes, alcohol units, other drugs used, education, and employment status.

Table 3: **Risk for first-episode psychosis for each measure of cannabis exposure**

cannabis (n=775 [data for employment history was missing for five participants, OR 0·93, 95% CI 0·67–1·52, p=0·569). Individuals who started using cannabis at ages younger than 15 years had modestly, but significantly, increased risk of psychotic disorders compared with those who never used cannabis (table 3). People who used cannabis or skunk every day were both roughly three times more likely to have a diagnosis of a psychotic disorder than were those who never used cannabis (table 3).

We used logistic regression (n=775) to test whether the composite cannabis exposure measure predicted risk of psychotic disorder more accurately than the individual markers, frequency of cannabis use and most used type of cannabis, alone. Individuals who mostly used low-potency (hash-like) cannabis occasionally (p=0·493), at weekends (p=0·102), or daily (p=0·626) had no increased likelihood of psychotic disorders compared with those who never used cannabis (figure 2).

Compared with those who never used cannabis, individuals who mostly used skunk-like cannabis were nearly twice as likely to be diagnosed with a psychotic disorder if they used it less than once per week (p=0·020), almost three times as likely if they used it at weekends (p=0·008), and more than five times as likely if they were daily users (p=0·001; figure 2).

Based on the estimated adjusted OR for daily cannabis use (3·04, 95% CI 1·91–7·76), we calculated that, if we assumed causality, 19·3% (13·1–27·0) of psychotic disorders in the study population were attributable to exposure to daily cannabis use. The PAF of psychotic disorders in the study population that were attributable to high potency cannabis use was 24·0% (17·4–30·6) and the PAF for the two exposures combined, skunk use every day, was 16·0% (14·0–20·3; table 4). If causality is assumed, this finding suggests that skunk alone was responsible for the largest proportion of new cases (24%) of psychotic disorder in the study population, an effect driven by its high prevalence among patients with first-episode psychosis who used cannabis (218 [53%] of 410 patients).

Discussion

The results of our study support our previous conclusions from analysis of part of the sample;[8] use of high-potency cannabis (skunk) confers an increased risk of psychosis compared with traditional low-potency cannabis (hash). Additionally, because of the increased sample size in the present study, we were able to combine information on frequency of use and type of cannabis used into a single measure. This combined measure suggested that the strongest predictor of case-control status (ie, predictor of whether a random individual would be case or control) was daily-skunk use. Figure 2, which shows the adjusted ORs for psychotic disorders for each of the composite cannabis exposure measure groups, shows how the ORs for skunk users increase with the frequency of use.

Samples of skunk seized in the London area in 2005,[13] 2008,[14] and more recently, as reported by Freeman and colleagues,[16] contained more THC than did samples of hash, and virtually no cannabidiol. Use of cannabis with a high concentration of THC might have a more detrimental effect on mental health than use of a weaker form. Indeed, in line with epidemiological evidence,[2,3] the results of experimental studies[17,18] that investigated the acute effects of intravenous administration of THC in non-psychotic volunteers showed that the resulting psychotic symptoms were dependent on the dose. Furthermore, the scarcity of cannabidiol in skunk-like cannabis might also be relevant because evidence suggests that cannabidiol ameliorates the psychotogenic effect of THC and might even have antipsychotic properties.[19,20] The presence of cannabidiol might explain our results, which showed that hash users do not have any increase in risk of psychotic disorders compared with non-users, irrespective of their frequency of use. Morgan and colleagues[21] previously reported that, in healthy volunteers who smoked cannabis, individuals with

hair traces of THC and cannabidiol had fewer schizophrenia-like symptoms than those with hair traces of THC only.

In our results, a combined measure of exposure to cannabis, daily use of high-potency cannabis, predicted a greater risk of psychotic disorders than did the single measures of either frequency or potency. However, a simple yes-or-no question of whether people use skunk might be more useful to identify those at increased risk to develop psychosis because of their cannabis use. In view of the high prevalence of skunk use in our study population, if a causal role for cannabis is assumed, skunk use alone was responsible for 24% of those adults presenting with first-episode psychosis to the psychiatric services in south London.

South London has one of the highest recorded incidence rates of psychosis in the UK.[22] Boydell and colleagues[23] showed that the incidence of schizophrenia had doubled since 1965,[24] and that one possible contribution to this was the increase in cannabis use among individuals who developed schizophrenia. In the present study, we identified an increased estimate for the PAF accounted for by cannabis (24%) compared with previous studies, which reported PAFs of 6·2% in Germany,[25] 8% in New Zealand,[26] and 13·3% in Holland.[5] This finding could be caused by, not only the greater use of cannabis, but also the greater use of high-potency (skunk-like) cannabis in south London than in these other countries in earlier periods.[27]

Hickman and colleagues[6] suggested that the number of people who need to be treated to stop their cannabis use to prevent one case of schizophrenia is large, but would become substantially lower if more was understood about which individuals are at greatest risk because of their pattern of use or their susceptibility to psychosis.[6] In relation to susceptibility to schizophrenia, Henquet and colleagues[25] calculated that the PAF for individuals in the general population with a predisposition for psychosis at baseline was more than double (14·2%) that of the total population (6·2%). Our data suggest that the potency of the cannabis used also needs to be taken into account in calculations of the PAF.

The strategy we used for control recruitment, based on a variety of advertising strategies rather than on random selection, might have biased the findings. However, the final sample of controls was similar, according to the last UK census data, to the population from which the cases were drawn. Moreover, rather than this approach undersampling individuals who used cannabis, the proportion of controls with a history of cannabis use (63%) was more than the national average (40%) for similar age groups,[28] showing the high prevalence of cannabis use in south London. Furthermore, if we had oversampled individuals who used cannabis, this oversampling would have caused underestimation of the effects of cannabis use on risk of psychotic disorders.

A theoretical explanation of why skunk might have been preferred by patients with first-episode psychosis is that, when they began to experience their illness prodrome, these individuals might have sought increased concentrations of THC to self-medicate. However, experimental studies show that THC induces psychotic symptoms, while cannabidiol ameliorates them and reduces anxiety.[16–19] That people who already have prodromal symptoms would choose a type of cannabis that is high in THC and has little cannabidiol (such as skunk), which might exacerbate their symptoms, rather than a cannabidiol-containing type (such as hash), would seem counterintuitive.

A possible limitation of our study is the absence of data on number of joints or grams used per day. However, because we collected information about use over a period of years and not about present use, the reliability of such detailed information would probably have been confounded by recall bias to a greater extent than was the general description of pattern of use that we obtained. The fact that we were able to collect detailed information on other environmental factors and control for their potential confounding effects is a key strength of our study.

Our findings show the importance of raising public awareness of the risk associated with use of high-potency cannabis (panel), especially when such varieties of cannabis are becoming more available.[29] The worldwide

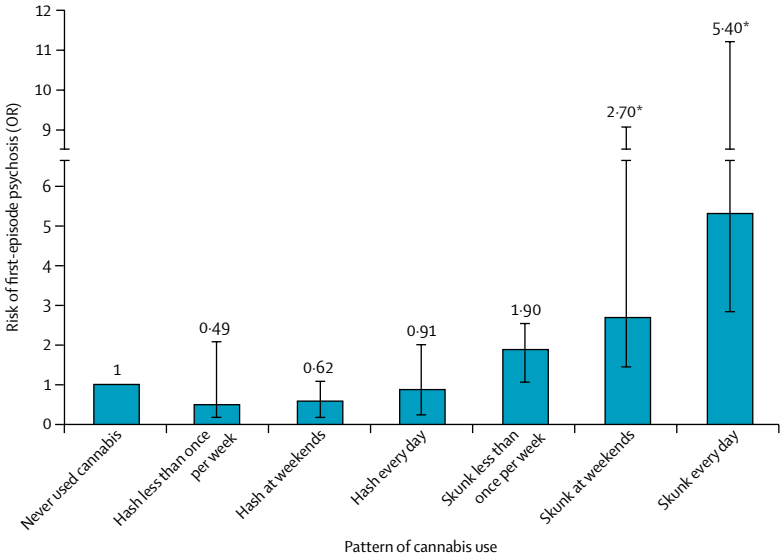

Figure 2: **Probability of individuals having a psychotic disorder by pattern of cannabis use**
OR adjusted for age, gender, ethnic origin, education, employment status, and tobacco use. OR=odds ratio. *p<0·05.

	Odds ratio* (95% CI)	Prevalence of exposure in patients with first-episode psychosis	Population attributable fraction (95% CI)
Daily cannabis use	3·04 (1·91–7·76)	123/410 (30%)	19·3% (13·1–27·0)
Skunk use	2·91 (1·52–3·60)	218/410 (53%)	24·0% (17·4–30·6)
Skunk use every day	5·40 (2·80–11·30)	103/410 (25%)	16·0% (14·0–20·3)

*Adjusted for age, gender, ethnic origin, number of cigarettes, alcohol units, other drugs used, level of education, and employment status.

Table 4: **Population attributable fraction for daily use of cannabis, skunk use, and skunk use every day**

Panel: Research in context

Systematic review

We searched PubMed for studies that estimated the effect of cannabis use on the number of new cases of psychosis arising in specific populations, using both the terms "population attributable fraction", and "number needed to treat". We also searched for studies that investigated the association between the "high potency and/or skunk" type of cannabis and psychosis. We included all studies available on PubMed until Sept 31, 2014. We identified three studies,[7,8,16] all of which met our inclusion criteria.

Interpretation

The association between cannabis use and increased risk of developing schizophrenia-like psychosis has been consistently reported by prospective epidemiological studies.[2,3] Our previous study was the first to show that use of high-potency (skunk-like) cannabis carries the highest risk for psychotic disorders.[8] In the present larger sample analysis, we replicated our previous report and showed that the highest probability to suffer a psychotic disorder is in those who are daily users of high potency cannabis. Indeed, skunk use appears to contribute to 24% of cases of first episode psychosis in south London. Our findings show the importance of raising awareness among young people of the risks associated with the use of high-potency cannabis. The need for such public education is emphasised by the worldwide trend of liberalisation of the legal constraints on cannabis and the fact that high potency varieties are becoming much more widely available. Finally, in both primary care and mental health services, a simple yes-or-no question of whether people use skunk might be more useful to identify those at increased risk to develop psychosis because of their cannabis use.

trend of liberalisation of the legal constraints on the use of cannabis further emphasises the urgent need to develop public education to inform young people about the risks of high-potency cannabis.

Contributors

In collaboration with the Genetics and Psychosis Study (VM, TRM, SAS, MR, AM, JO'C, CI, PD, CP) and the PUMP study (FG, ZA, PG-S) teams, MDF, AT, and SAS collected the data and MDF prepared the data for the analysis. MDF did the data analysis with CM. MB and FB contributed to the data entry. ML and RMM supervised MDF in the interpretation of the results. EC and SF contributed to the literature review and to the selection of the references. ASD and JP reviewed the manuscript and contributed to its final draft. All authors had full access to all data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interests

RMM reports honoraria from Otsuka, Lundbeck, and Janssen, which he received for lecturing on the report of the Schizophrenia Commission. All other authors declare no competing interests.

Acknowledgments

The study was funded by the UK National Institute of Health Research (NIHR) Specialist Biomedical Research Centre for Mental Health, the South London and Maudsley (SLaM) NHS Foundation, the Institute of Psychiatry of King's College London, the Psychiatry Research Trust, Maudsley Charity Research Fund, and the European Community's Seventh Framework Programme (grant agreement No. HEALTH-F2-2009-241909 [project EU-GEI]). The study was supported by the Genetics and Psychosis (GAP) and Physical Health and Substance Use Measures in First Onset Psychosis (PUMP) study teams of the Institute of Psychiatry, King's College London, and SLaM.

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