Psychological Medicine (2008), **38**, 1251–1256. © 2008 Cambridge University Press
doi:10.1017/S0033291708003474 Printed in the United Kingdom

ORIGINAL ARTICLE

Cannabis use and genetic predisposition for schizophrenia: a case-control study

W. Veling[1,2]*, J. P. Mackenbach[2], J. van Os[3,4] and H. W. Hoek[1,5,6]

[1] *Parnassia Psychiatric Institute, The Hague, The Netherlands*
[2] *Erasmus Medical Center, Department of Public Health, Rotterdam, The Netherlands*
[3] *European Graduate School of Neuroscience and South Limburg Mental Health Research and Teaching Network, Maastricht University, Maastricht, The Netherlands*
[4] *Division of Psychological Medicine, Institute of Psychiatry, London, UK*
[5] *Columbia University, Department of Epidemiology, New York, NY, USA*
[6] *University Medical Center Groningen, Department of Psychiatry, Groningen, The Netherlands*

Background. Cannabis use may be a risk factor for schizophrenia. Part of this association may be explained by genotype–environment interaction, and part of it by genotype–environment correlation. The latter issue has not been explored. We investigated whether cannabis use is associated with schizophrenia, and whether gene–environment correlation contributes to this association, by examining the prevalence of cannabis use in groups with different levels of genetic predisposition for schizophrenia.

Method. Case-control study of first-episode schizophrenia. Cases included all non-Western immigrants who made first contact with a physician for schizophrenia in The Hague, The Netherlands, between October 2000 and July 2005 ($n=100$; highest genetic predisposition). Two matched control groups were recruited, one among siblings of the cases ($n=63$; intermediate genetic predisposition) and one among immigrants who made contact with non-psychiatric secondary health-care services ($n=100$; lowest genetic predisposition). Conditional logistic regression analyses were used to predict schizophrenia as a function of cannabis use, and cannabis use as a function of genetic predisposition for schizophrenia.

Results. Cases had used cannabis significantly more often than their siblings and general hospital controls (59, 21 and 21% respectively). Cannabis use predicted schizophrenia [adjusted odds ratio (OR) cases compared to general hospital controls 7.8, 95% confidence interval (CI) 2.7–22.6; adjusted OR cases compared to siblings 15.9 (95% CI 1.5–167.1)], but genetic predisposition for schizophrenia did not predict cannabis use [adjusted OR intermediate predisposition compared to lowest predisposition 1.2 (95% CI 0.4–3.8)].

Conclusions. Cannabis use was associated with schizophrenia but there was no evidence for genotype–environment correlation.

Received 3 October 2007; Revised 25 March 2008; Accepted 31 March 2008; First published online 19 May 2008

Key words: Cannabis, gene–environmental correlation, schizophrenia.

Introduction

Several studies have reported that exposure to cannabis during adolescence and young adulthood increases the risk for schizophrenia later in life (Arseneault *et al*. 2004). Recent meta-analyses of prospective studies yielded pooled odds ratios (ORs) of the association between cannabis use and psychosis of 2.1 [95% confidence interval (CI) 1.7–2.5] (Henquet *et al*. 2005*b*) and 1.4 (95% CI 1.2–1.7) (Moore *et al*. 2007). Although these results are suggestive of an association between cannabis use and psychosis, it has been argued that caution is required in the interpretation of such findings, as they are derived from bias- and confounding-prone observational studies and questions remain with regard to specificity and the possibility of reverse causation (MacLeod 2007; Collip *et al*. 2008). The issue of whether cannabis use is a cause of schizophrenia has not been settled, and there is evidence of underlying heterogeneity of the relative risk associated with other vulnerability factors (Verdoux *et al*. 2003; Henquet *et al*. 2005*a*). In particular, there may be an interplay between genetic liability for psychosis and cannabis use with regard to the development of psychosis (Henquet *et al*. 2005*a*). There are two main types of gene–environment interplay.

* Address for correspondence: W. Veling, M.D., Ph.D., Parnassia Psychiatric Institute, Department of Research, Mangostraat 15, 2552 KS The Hague, The Netherlands.
(Email: w.veling@parnassia.nl)

First, genetic differences between people may change sensitivity to environmental influences (genotype–environment interaction, or G × E) (Eaves *et al*. 2005). Recent studies reported that a functional polymorphism in the catechol-*O*-methyltransferase (*COMT*) gene moderated the effect of cannabis use on the risk for psychosis (Caspi *et al*. 2005; Henquet *et al*. 2006), suggesting that G × E may play a role. Second, genetic differences may affect the environments people choose or experience (genotype–environment correlation, or rGE) (Eaves *et al*. 2005). Genetic predisposition for psychosis thus may directly affect cannabis use. This is an important methodological issue because, in the case of rGE, the association between cannabis and psychotic illness may be considered an epiphenomenon resulting from the 'true' association between genetic liability for psychosis and cannabis (Collip *et al*. 2008). Caspi *et al*. (2005) did not find evidence that the specific $COMT^{val158met}$ polymorphism predisposes individuals to initiate cannabis use but there is conflicting evidence that general psychometric psychosis liability may predict future cannabis use (Stefanis *et al*. 2004; Ferdinand *et al*. 2005; Henquet *et al*. 2005*a*). Effect sizes were small and not consistently statistically significant, and because in these studies liability for psychosis was defined as high scores on paranoid ideation and psychoticism at baseline, the association with cannabis use may indicate not only rGE but also self-medication for distress or indeed an early effect of cannabis on symptoms of psychosis.

We conducted a case-control study of first-episode schizophrenia in The Hague, The Netherlands, and included three groups with a different genetic predisposition for psychosis: first-episode schizophrenia patients (highest predisposition), their siblings (intermediate predisposition), and matched general hospital controls (lowest predisposition). We excluded control subjects who had ever had any psychotic symptom, and assessed lifetime cannabis use among participants. Two questions were addressed: (1) is cannabis use associated with the development of schizophrenia (that is, do cases use cannabis more often than both control groups before illness onset) and (2) is there evidence for rGE, independent of phenotypic expression of predisposition for psychosis (that is, do siblings use cannabis more often than general hospital controls)?

Method

Participants

Cases

This paper used data from a study among ethnic minorities in The Hague. All first- or second-generation immigrants from non-Western countries (of whom 85% were from Surinam, Morocco, Turkey or Netherlands-Antilles), aged 18–54 years, who made first contact with a physician in The Hague for a psychotic disorder and received a diagnosis of a schizophrenia spectrum disorder (DSM-IV: schizophrenia, schizophreniform disorder, schizo-affective disorder) between 1 October 2000 and 1 July 2005 were eligible for the study. Case-finding procedures and the diagnostic protocol of the study have been described elsewhere (Veling *et al*. 2006). If the patients had been adopted as a child, they were excluded ($n = 4$).

Controls

For each patient, two control subjects were recruited, matched for 5-year age group, sex and ethnicity (including first- or second-generation immigrant status). They were screened for psychotic symptoms (see Measures) and were excluded if these were present ($n = 5$). The first control group consisted of siblings of the patients. If a patient had more than one sibling, the same-sex sibling closest in age was selected. The second control group was recruited among the general ethnic minority population of The Hague. To minimize selection bias as a result of pathways to care, the controls were selected from immigrants who made contact with non-psychiatric secondary health-care services. Controls were recruited from the out-patient departments of Internal Medicine and Surgery of a general hospital.

All participants gave written informed consent for the study, which was approved by the local ethics committee.

Measures

In the control subjects, the psychosis section of the Composite International Diagnostic Interview (CIDI), version 2.1 (Smitten *et al*. 1998), was administered. Lifetime use of cannabis and other substances was assessed with the section on drugs of the Comprehensive Assessment of Symptoms and History (CASH; Andreasen *et al*. 1992). Participants were instructed to answer questions about their pattern of use before illness onset, the date of which was determined first. Individuals with lifetime use of five times or more were considered as exposed. Other substances were divided into two groups: (1) psychostimulants and cocaine (substances sharing the potential to cause psychotic symptoms by influencing dopamine release) and (2) opiates and psychedelic drugs. Information was noted on marital status (single or else). Socioeconomic status was assessed using level of education (no or primary, secondary, or higher education) and employment status (unemployed or else).

Table 1. *Characteristics of study sample, by matched case-control status*[a]

	Cases ($n=100$)	General hospital controls ($n=100$)	Sibling controls ($n=63$)
Age, mean (S.D.)	26.6 (6.7)	27.2 (7.2)	26.5 (8.5)
Male sex, *n* (%)	74 (74)	72 (72)	29 (46)**
Ethnicity, *n* (%)			
Moroccan	29 (29)	30 (30)	20 (32)
Turkish	19 (19)	20 (20)	12 (19)
Surinamese	32 (32)	34 (34)	21 (33)
Other non-Western	20 (20)	17 (17)	10 (16)
Second generation, *n* (%)	36 (36)	35 (35)	28 (44)
Single marital status, *n* (%)	72 (72)	46 (46)**	37 (59)**
Level of education, *n* (%)			
No/Primary	9 (9)	11 (11)	6 (10)
Secondary	77 (77)	63 (63)	37 (59)
Higher	13 (13)	26 (26)	21 (33)
Unemployed, *n* (%)	17 (17)	9 (9)	3 (5)*
Other drug use, *n* (%)[b]	20 (20)	4 (4)**	5 (8)*
Cocaine and/or psychostimulants	19 (19)	2 (2)	4 (6)
Opiates and/or psychedelic drugs	1 (1)	1 (1)	0 (0)
Not specified	1 (1)	1 (1)	1 (2)

S.D., Standard deviation.

[a] Differences between cases and other groups tested by the Wald test, conditional logistic regression analysis.

[b] Lifetime use, defined as more than five times. One case used both cocaine and heroin.

* $p<0.05$, compared to cases, ** $p<0.005$.

Statistical analysis

Stata Statistical Software release 9.2 (Stata Corporation, College Station, TX, USA) was used for all statistical analyses. To answer the first research question we calculated ORs and 95% CIs for schizophrenia, with cannabis use as the independent variable. Conditional (fixed-effects) logistic regression techniques were required to take the matched case-control design into account. Comparisons were made between cases and general hospital controls (100 pairs), and between cases and sibling controls (63 pairs). To investigate genotype–environment correlation, siblings were compared to general hospital controls, with conditional logistic regression analysis, including cannabis use as dependent variable and genetic predisposition for schizophrenia as predictor of cannabis use. All associations were adjusted (through matching or as covariates in the model) for age, sex, marital status, level of education, unemployment, and the two groups of other drug use.

Results

Of the 146 patients who were eligible for the study, two patients died before the study commenced. Twenty-six patients could not be interviewed because they had remigrated to their home country ($n=5$), they were too ill during the entire study period ($n=8$) or there was no current address available ($n=13$). Of the 118 patients who were contacted, 18 refused to participate. Thus, 100 patients were interviewed. Of the 168 subjects in the general hospital control group who were matched to the schizophrenia patients, four subjects were physically too ill to be interviewed, one was mentally handicapped, three were excluded because they had a psychotic disorder, and 60 refused to participate. For 15 patients there was no sibling available because all siblings were too young or lived abroad, patients had no sibling, or patients did not know their current address. Nine patients refused permission to contact their siblings, two patients only had a sibling who had psychotic symptoms. For 14 of the remaining 74 patients, the sibling who was matched to the case refused to participate; in three of these cases, another sibling agreed to participate. Thus, for 63 cases, a sibling could be interviewed. Characteristics of the study sample are shown in Table 1.

Fifty-nine per cent of the cases, 21% of their siblings and 21% of the general hospital controls had used

https://doi.org/10.1017/S0033291708003474 Published online by Cambridge University Press

Table 2. *Odds ratios (ORs) of schizophrenia, by cannabis use*[a]

	Cannabis use[b] *n* (%)	Unadjusted OR (95% CI)	Adjusted[c] OR (95% CI)
Cases ($n=100$)	59 (59)	6.4 (2.9–14.3)	7.8 (2.7–22.6)
General hospital controls ($n=100$)	21 (21)	1.0	1.0
Cases ($n=63$)	43 (68)	30.0 (4.1–220.0)	15.9 (1.5–167.1)
Sibling controls ($n=63$)	13 (21)	1.0	

CI, Confidence interval.
[a] Using conditional logistic regression.
[b] Lifetime use, defined as more than five times.
[c] Adjusted for use of psychostimulants and cocaine, use of opiates and psychedelic drugs, (sex), marital status, level of education and unemployment.

Table 3. *Odds ratios (ORs) of cannabis use*[a]*, by genetic predisposition for schizophrenia*[b]

	Unadjusted OR (95% CI)	Adjusted[c] OR (95% CI)
Highest predisposition ($n=100$)	7.6 (3.4–17.0)	9.8 (2.9–32.6)
Intermediate predisposition ($n=63$)	0.8 (0.4–1.9)	1.2 (0.4–3.8)
Lowest predisposition ($n=100$)	1.0	1.0

CI, Confidence interval.
[a] Lifetime use, defined as more than five times.
[b] Using conditional logistic regression.
[c] Adjusted for use of psychostimulants and cocaine, use of opiates and psychedelic drugs, sex, marital status, level of education and unemployment.

cannabis (Table 2). Conditional logistic regression analyses showed that the differences between cases and the other groups were statistically significant. After adjustment for confounders, including the variable of psychostimulant and cocaine use, cannabis use remained a statistically significant predictor of schizophrenia (Table 2).

There was no difference between siblings and matched general hospital controls in prevalence of cannabis use (Table 2). Genetic predisposition for schizophrenia did not predict cannabis use, as the OR of cannabis use for siblings *versus* general hospital controls was 0.8 (95% CI 0.4–1.9) before and 1.2 (95% CI 0.4–3.8) after adjustment (Table 3).

Discussion

Cannabis use was associated with schizophrenia in this case-control study of first-episode schizophrenia. Cases had used cannabis approximately three times more often than their siblings and matched general hospital controls. Sibling controls had not used cannabis more often than general hospital controls, despite their higher genetic predisposition for schizophrenia.

Our results add to the evidence that cannabis use is associated with an increased risk of schizophrenia (Arseneault *et al*. 2004). The magnitude of the effect was substantially larger than that calculated in the meta-analysis of results from prospective studies (Henquet *et al*. 2005*b*). Although patients had been instructed to report on cannabis use before illness onset, it is possible that they did not recognize early prodromal symptoms as such, creating the possibility that in some patients the period of cannabis assessment may have overlapped with the onset of schizophrenia. The association between cannabis and psychosis may be bidirectional, that is cannabis may be not only a causal factor in the pathway to schizophrenia but also used as self-medication for distress or early prodromal symptoms, as has been suggested by previous findings (Ferdinand *et al*. 2005).

It is very unlikely that the association between cannabis and schizophrenia can be explained by genotype–environment correlation. Unlike other studies (Verdoux *et al*. 2003; Henquet *et al*. 2005*a*), we used unaffected siblings and unrelated controls who had never had any psychotic symptom to classify the degree of genetic predisposition for schizophrenia rather than measures of psychoticism or delusional ideation. This allowed us to investigate genotype–environment correlation independent of a possible self-medication effect. The comparison between siblings and unrelated controls showed that higher genetic predisposition for schizophrenia did not lead to a higher rate of lifetime cannabis use.

The pattern of results with regard to schizophrenia liability and psychostimulants or cocaine was similar to that of cannabis: 19% ($n=19$) of cases used *versus* only 2% ($n=2$) in controls and 6% ($n=4$) in siblings. Although the number of individuals using these drugs was too small for formal statistical comparison, the findings are very similar to those described for cannabis with cases having much higher rates than both controls and siblings.

Methodological issues

Cannabis exposure was defined as use of cannabis $\geqslant$ five times, but the effect of cannabis may be different

https://doi.org/10.1017/S0033291708003474 Published online by Cambridge University Press

in someone who used only five times compared to a regular dependent user. When we analysed the group of daily users separately, ORs of schizophrenia were even higher [adjusted OR cases compared to general hospital controls 13.6 (95% CI 2.8–66.4); adjusted OR cases compared to siblings 29.2 (95% CI 1.6–517.3)]. In addition, there was no evidence that the OR of daily cannabis use for siblings compared to controls was increased [adjusted OR 0.3 (95% CI 0.02–5.2)]. These findings similarly indicate the absence of a gene–environment correlation and suggest a dose–response relationship between cannabis use and schizophrenia risk, although the wide CIs preclude firm conclusions.

A limitation of the study is that we did not have reliable information on age at first cannabis use and duration of use, as these factors may also influence the association between cannabis and schizophrenia.

This study only included first- and second-generation non-Western immigrants, which raises the question of whether the findings can be generalized across (other) ethnic groups. It is conceivable that the correlation between genetic factors and cannabis use is different in majority and minority populations, or that some ethnic groups may be more vulnerable to the psychotogenic effects of cannabis than other groups. We did not have data on the Dutch majority population, but when we stratified for ethnicity in our data, the associations between cannabis and (predisposition for) schizophrenia were very similar in the Surinamese, Turkish and Moroccan groups (results available on request).

Difficulties in the recruitment of siblings may have caused selection bias, as the siblings who refused to participate may have used cannabis more often than those who agreed to be interviewed. However, although the difference between cases and siblings in the prevalence of cannabis use was large, there was no suggestion of a difference between the two control groups, making it unlikely that selection bias could have had a major impact on the results. Even if we assumed that all refusing sibs had been cannabis users, the difference in cannabis use between siblings and controls would not have been statistically significant [the rates would have been 35% and 21% respectively, unadjusted OR 1.8 (95% CI 0.9–3.9)]. Instead, the large difference between cases and siblings in the rate of cannabis use is compatible with an underlying mechanism of gene–environment interaction, suggesting that genetic predisposition alone may not be sufficient to cause psychotic disorder.

Drug use was assessed with information provided by the participants themselves. This may have led to under-reporting, although in The Netherlands the attitude towards substance use is quite open. In addition, the researchers were not involved with patients' treatment, and did not provide any information to the physician responsible without the patients' consent.

Participants were asked whether they had ever used drugs before illness onset. There may have been recall bias as a result of this retrospective assessment, particularly in the group of cases, because impaired cognitive functioning is one of the features of schizophrenia (Murray *et al*. 2003). If anything, however, this is likely to have led to underestimation of the prevalence of cannabis use in cases.

The general hospital controls may not have been representative of the general immigrant population, but the choice for a control group selected from immigrants who made contact with non-psychiatric secondary health-care services minimized selection bias as a result of pathways to care, as the schizophrenia cases were also recruited from secondary psychiatric services. Moreover, the very diverse complaints for which the controls made contact (ranging from fractures to anal fissures) makes it unlikely that their somatic illness would be related to cannabis use.

Conclusions

Our findings support the hypothesis that cannabis use is a risk factor for schizophrenia, and suggest that genetic predisposition for schizophrenia does not increase the risk of cannabis use. Associations between cannabis use, genetic predisposition for psychosis, and schizophrenia cannot be attributed to genotype–environment correlation but are most probably due to interactions between genetic factors and cannabis. Replication of these findings in larger samples with other direct and indirect measures of genetic psychosis liability is needed to enable definite conclusions to be drawn.

Acknowledgments

This study was supported by a research grant from the Netherlands Organization for Health Research and Development, grant number 100-002-009.

Declaration of Interest

None.

References

Andreasen NC, Flaum M, Arndt S (1992). The Comprehensive Assessment of Symptoms and History (CASH). An instrument for assessing diagnosis and psychopathology. *Archives of General Psychiatry* **49**, 615–623.

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

Caspi A, Moffitt TE, Cannon M, McClay J, Murray R, Harrington H, Taylor A, Arseneault L, Williams B, Braithwaite A, Poulton R, Craig IW (2005). Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-*O*-methyltransferase gene: longitudinal evidence of a gene × environment interaction. *Biological Psychiatry* **57**, 1117–1127.

Collip D, Myin-Germeys I, Van Os J (2008). Does the concept of 'sensitization' provide a plausible mechanism for the putative link between the environment and schizophrenia? *Schizophrenia Bulletin* **34**, 220–225.

Eaves L, Chen S, Neale M, Maes HH, Silberg J (2005). Questions, models, and methods in psychiatric genetetics. In *Psychiatric Genetics* (ed. K. S. Kendler and L. Eaves), pp. 19–94. American Psychiatric Publishing: Washington, DC.

Ferdinand RF, Sondeijker F, Van der Ende J, Selten JP, Huizink A, Verhulst FC (2005). Cannabis use predicts future psychotic symptoms, and vice versa. *Addiction* **100**, 612–618.

Henquet C, Krabbendam L, Spauwen J, Kaplan C, Lieb R, Wittchen HU, van Os J (2005*a*). Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. *British Medical Journal* **330**, 11–14.

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.

Henquet C, Rosa A, Krabbendam L, Papiol S, Fananas L, Drukker M, Ramaekers JG, van Os J (2006). An experimental study of catechol-*O*-methyltransferase Val158Met moderation of delta-9-tetrahydrocannabinol-induced effects on psychosis and cognition. *Neuropsychopharmacology* **31**, 2748–2757.

MacLeod J (2007). Cannabis use and symptom experience amongst people with mental illness: a commentary on Degenhardt *et al*. *Psychological Medicine* **37**, 913–916.

Moore THM, Zammit S, Lingford-Hughes A, Barnes TRE, Jones PB, Burke M, Lewis G (2007). Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet* **370**, 319–328.

Murray RM, Jones PB, Susser E, Van Os J, Cannon M (eds) (2003). *The Epidemiology of Schizophrenia*. Cambridge University Press: Cambridge.

Smitten MH, Smeets RMW, Van den Brink W (1998). *Composite International Diagnostic Interview* (*CIDI*), *Version 2.1*. World Health Organization: Amsterdam.

Stefanis NC, Delespaul P, Henquet C, Bakoula C, Stefanis CN, van Os J (2004). Early adolescent cannabis exposure and positive and negative dimensions of psychosis. *Addiction* **99**, 1333–1341.

Veling W, Selten JP, Veen N, Laan W, Blom JD, Hoek HW (2006). Incidence of schizophrenia among ethnic minorities in the Netherlands: a four-year first-contact study. *Schizophrenia Research* **86**, 189–193.

Verdoux H, Gindre C, Sorbara F, Tournier M, Swendsen JD (2003). Effects of cannabis and psychosis vulnerability in daily life: an experience sampling test study. *Psychological Medicine* **33**, 23–32.