Tests of causal linkages between cannabis use and psychotic symptoms

David M. Fergusson, L. John Horwood & Elizabeth M. Ridder

Christchurch Health and Development Study, Christchurch School of Medicine, Christchurch, New Zealand

Correspondence to:
Professor David Fergusson
Christchurch Health and Development Study
Department of Psychological Medicine
Christchurch School of Medicine and Health Sciences
PO Box 4345
Christchurch
New Zealand
Tel: 64 3372 0406
Fax: 64 3372 0405
E-mail: david.fergusson@chmeds.ac.nz

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ABSTRACT

Aim To examine possible causal linkages between cannabis use and psychosis using data gathered over the course of a 25-year longitudinal study.

Design A 25-year longitudinal study of the health, development and adjustment of a birth cohort of 1265 New Zealand children (635 males, 630 females).

Setting The Christchurch Health and Development Study, a general community sample.

Participants A total of 1055 participants from the Christchurch Health and Development Study (CHDS) cohort for whom data on cannabis use and psychotic symptoms were available on at least one occasion from 18, 21 and 25 years.

Measurements As part of this study, data were gathered on frequency of cannabis use and psychotic symptoms at ages 18, 21 and 25 years.

Findings Regression models adjusting for observed and non-observed confounding suggested that daily users of cannabis had rates of psychotic symptoms that were between 1.6 and 1.8 times higher ($P < 0.001$) than non-users of cannabis. Structural equation modelling suggested that these associations reflected the effects of cannabis use on symptom levels rather than the effects of symptom levels on cannabis use.

Conclusions The results of the present study add to a growing body of evidence suggesting that regular cannabis use may increase risks of psychosis. The present study suggests that: (a) the association between cannabis use and psychotic symptoms is unlikely to be due to confounding factors; and (b) the direction of causality is from cannabis use to psychotic symptoms.

KEYWORDS Cannabis, longitudinal study, psychosis, psychotic symptoms, structural equation modelling.

INTRODUCTION

Over the last decade there has been growing research into the linkages between the use of cannabis and the development of psychosis and psychotic symptoms (for reviews see [1–3]). This research has resulted in a growing body of evidence that suggests that the use (and particularly heavy use) of cannabis may be associated with increased risks of psychosis or psychotic symptoms. This conclusion has been supported by evidence from a series of longitudinal studies, all of which have found increased risks of psychosis or psychotic symptoms among cannabis users after control for confounding factors [4–7]. Epidemiological research linking cannabis use and psychosis has also been underwritten by laboratory-based research examining the psychogenic effects of cannabis (e.g. [8–11]) and by increasing evidence on the effects of cannabis on brain chemistry and functioning (e.g. [12–14]). Collectively, this evidence has provided growing support for the hypothesis that heavy cannabis use may precipitate or exacerbate psychosis or psychotic symptoms in vulnerable individuals. None the less, considerable uncertainly still remains about this topic and there is a clear need for further evidence to confirm the causal

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contribution of cannabis to psychosis and to develop a clearer understanding of the underlying pathways by which the consumption of cannabis may be transformed into an increased susceptibility to psychosis. The aims of this paper are to test further the causal linkages between cannabis use and psychotic symptoms by applying statistical modelling methods to the results of a longitudinal study of cannabis use in a birth cohort studied into adulthood. The background to this analysis is developed below.

Key issues in determining the causal role of cannabis in psychosis

It has now been well established that the use of cannabis is statistically linked to increased risks of psychosis. In a review of five studies, Arsenault *et al*. [1] found that all the studies were in agreement that the use of cannabis increases the risk of subsequent schizophrenia and psychotic symptoms. Similarly, in a parallel review of this topic Smit *et al*. [3] concluded that cannabis use is associated with the onset of psychosis, especially in those prone to developing schizophrenia, and also makes a unique contribution to the risk of developing schizophrenia. However, the extent to which these statistical associations reflect a cause and effect association in which the consumption of cannabis leads to an increased susceptibility to psychosis/psychotic symptoms remains open to debate. There are two potential major threats to validity that need to be addressed.

Residual confounding

The largest threat to the validity of causal conclusions in this area comes from the possibility of uncontrolled residual confounding. In reviewing this issue, Macleod *et al*. [15] concluded that while a number of studies had shown linkages between cannabis use and mental health that persisted following control for confounders the possibility remained that these linkages reflected uncontrolled residual confounding rather than the causal effects of cannabis use on psychotic symptoms. There is thus a need for more searching methods for controlling confounding factors.

Reverse causality

However, even if it were possible to establish that an association existed between cannabis use and psychosis net of confounders, this evidence would not establish the direction of causation. In particular, there are potentially two causal pathways that may link cannabis use and psychosis. First, cannabis use may lead (via changes in brain chemistry) to an increased susceptibility to psychotic symptoms. Alternatively, those developing psychosis may have an increased susceptibility to using cannabis as a consequence of their psychological state.

The above suggests that to clarify further the role of cannabis in the development of psychotic symptoms and psychosis there is a need for further research to address issues relating to the control of residual confounding and reverse causality in the association between cannabis use and psychosis. Below we describe methods using longitudinal data to address each of these problems.

Controlling residual confounding with the fixed effects regression model

Although it is often believed that epidemiological research can control only for the effects of observed confounders, in fact this is not strictly correct and there are a number of analytical approaches that permit the control of non-observed confounders in non-experimental research. Perhaps the best-known of these is the so-called discordant twin design, in which monozygotic twins who are discordant for some exposure variable (e.g. cannabis use) are compared on an outcome measure (e.g. psychosis). Because the twin pairs share both common genes and common environment, this comparison controls for these factors even though the common genes and common environment are not observed [16,17].

The principles underlying the discordant twin design can also be applied to longitudinal data on singletons via the fixed effects regression model. In particular, subject to the availability of longitudinal data, it proves possible to estimate the associations between a time-varying exposure variable (such as cannabis use) and a time-varying outcome measure (such as psychosis) net of any non-observed factors that are associated with the outcome and that may be correlated with the exposure variable [18]. The underlying logic of the fixed effects regression model is described later in Statistical methods. In effect, this model makes it possible to eliminate one major source of confounding from fixed factors. However, the model does not address the issue of confounders that may vary over time and to control for such confounding, the fixed effects model needs to be augmented by observed time-dynamic confounding factors.

Ascertaining causal direction using structural equation modelling

Establishing that cannabis use and psychosis are related, even following control for confounding, is an important step in ascertaining a causal relationship between cannabis use and psychosis. However, such analysis does not resolve the issue of the direction of causality between cannabis use and psychosis: does cannabis use cause psychosis or does psychosis lead to an increased use of cannabis?

Answering such questions proves to be difficult and even with well collected longitudinal data, establishing which factor is antecedent and which factor is consequent proves difficult [1,19]. Furthermore, there is a possibility that cannabis use and psychosis are related to each other reciprocally by a feedback loop in which the use of cannabis increases risks of psychosis while at the same time the onset of psychosis leads to an increased consumption of cannabis. Structural equation models provide one means of addressing such a complex issue by devising statistical models that permit reciprocal relationships between cannabis use and psychosis and using these models to provide a guide to probable patterns of causation. An account of the ways in which structural equation modelling may be employed to examine reciprocal pathways is given in the Statistical methods section of this paper.

Aims of the present study

The present study seeks to examine these issues using extensive data collected on the development of cannabis use and psychotic symptoms in a birth cohort of New Zealand young people studied throughout adolescence and young adulthood. The aims of this study were twofold:

1 To control the association between cannabis use and psychotic symptoms using a range of statistical methods including fixed effects regression to control for non-observed confounding factors.
2 To employ structural equation modelling methods to explore the direction of any causal influence between the use of cannabis and psychotic symptoms.

More generally, the aims of the paper are to apply complex multivariate methods to an extensive body of data on cannabis use and psychotic symptoms to address issues relating to both residual confounding and causal direction.

METHOD

Participants

The data described in this report were gathered during the course of the Christchurch Health and Development Study (CHDS). The CHDS is a longitudinal study of an unselected birth cohort of 1265 children (635 males, 630 females) born in the Christchurch (New Zealand) urban region in mid-1977. This cohort has now been studied at birth, 4 months, 1 year and at annual intervals to age 16 years, and again at ages 18, 21 and 25 years. As part of the study, information has been gathered from a range of sources including: parental interview, teacher reports, psychometric testing, self-reports, and medical and police records. The present analysis is based on a sample of 1055 participants for whom information on cannabis use and psychotic symptoms was available for at least one assessment from age 18, 21 or 25 years. All phases of data collection were subject to written, informed consent from study participants. The following measures were used in the analysis.

Psychotic symptomatology

At ages 18, 21 and 25 years, sample members were administered a comprehensive mental health interview designed to assess a number of aspects of the individual's mental health and psychosocial adjustment. As part of this interview, participants were questioned on current (over the past month) psychotic symptomatology using items from the Symptom Checklist 90 (SCL-90) [20]. A series of 10 items were selected as representative of psychotic symptoms [5]. These items spanned the following symptoms: hearing voices that other people do not hear; the idea that someone else can control your thoughts; other people being aware of your private thoughts; having thoughts that are not your own; having ideas and beliefs that others do not share; the idea that something is seriously wrong with your body; never feeling close to another person; the idea that something is wrong with your mind; feeling other people cannot be trusted; feeling that you are watched or talked about by others. Confirmatory factor analysis of the item set has shown previously that the items formed a unidimensional scale reflecting the extent of psychotic symptomatology [5]. Scale scores were estimated by summing the number of symptoms reported by each participant at each age. Reliability was assessed using coefficient alpha, $\alpha = 0.74$ (18 years), $\alpha = 0.73$ (21 years) and $\alpha = 0.75$ (25 years).

Frequency of cannabis use

At each assessment from 18 to 25 years, sample members were questioned about their use of cannabis use since the previous interview. As part of this questioning, information was obtained on the frequency of cannabis use over the previous 12-month period. This information was used to classify sample members on a five-point scale reflecting the average level of cannabis use throughout the year. This scale was: 1 = non-user; 2 = used cannabis on less than a monthly basis; 3 = used cannabis on at least a monthly basis; 4 = used cannabis on at least a weekly basis; 5 = used cannabis on a daily basis. To examine the accuracy of reports of cannabis use, data on the participant's cannabis use were also obtained from a nominated informant. There was good agreement between respondent and informant reports ($r = 0.68$; $P < 0.001$).

Time-dynamic covariate factors

To control the associations between cannabis dependence and psychotic symptoms for time-varying sources of confounding the following measures were selected from the database of the study.

Prior history of cannabis use/psychotic symptoms

To control for the individual's prior history of cannabis use and psychotic symptoms, measures of the frequency of cannabis use and psychotic symptoms at the time of the preceding assessment were included as confounding factors. Thus, for 18 years, psychotic symptoms and cannabis use at age 16 years were controlled, for 21 years psychotic symptoms and cannabis use at age 18 years were controlled and for 25 years psychotic symptoms and cannabis use at age 21 were controlled.

Concurrent/prior mental disorders

As part of the mental health interviews administered at ages 16, 18, 21 and 25 years, questioning was conducted to assess standardized diagnostic criteria for a range of mental disorders. At age 16, questioning was conducted using an interview that combined components of the Diagnostic Interview Schedule for Children [21], the Self-Report Delinquency Inventory [22], the Rutgers Alcohol Problems Index [23] and custom-written survey items to assess *Diagnostic and Statistical Manual* version III–revised (DSM-III-R) symptom criteria. From age 18 onwards the interview combined components of the Composite International Diagnostic Interview [24], the Self-Report Early Delinquency Scale [25] and custom-written survey items to assess relevant DSM-IV diagnostic criteria. Using these data, sample members were classified on the following DSM disorders at each age: major depression in the past 12 months; anxiety disorders (including generalized anxiety disorder, panic disorder/agoraphobia, social phobia and specific phobia); alcohol and illicit drug dependence in the past 12 months; current nicotine dependence; conduct and/or antisocial personality disorder. For the purposes of the present analysis, measures of both concurrently assessed disorders and disorders at the time of the previous assessment were included as covariates.

Other factors

Parallel to questioning on mental health, information was also obtained on other time-dynamic aspects of the individual's life-style, including the extent of affiliations with deviant peers and exposure to adverse life events. At each age sample members were questioned on a series of items concerning the extent to which their friends used or had problems associated with alcohol, tobacco or illicit drugs, had problems with aggression or were involved in criminal offending. These items were combined to derive a scale score measure of the extent of deviant peer affiliations at each age [26]. The reliability of all three measures, assessed using coefficient alpha, was 0.85. In addition, at each assessment sample members were questioned about exposure to adverse life events over the past 12 months using a scale based on the life events scale described by Henderson, Byrne & Duncan-Jones [27]. At each age, the number of life events reported was summed to provide a measure of the extent of adversity experienced in the previous 12 months.

Fixed covariate factors

A wide range of measures of social, family and individual functioning that were assessed prior to age 18 and were correlated with either cannabis use or psychotic symptoms were considered in the analysis. These factors included the following.

Measures of family socio-economic circumstances

(a) *Maternal education* at the time of the survey child's birth was classified in three levels according to the mother's highest level of educational attainment (no formal qualifications; high school qualifications; and tertiary qualifications). (b) *Maternal age* was coded in whole years at the time of the survey child's birth. (c) *Family socio-economic status* was assessed at the point of birth using the Elley–Irving [28] scale of socio-economic status for New Zealand. This index classifies families into six levels on the basis of paternal occupation. (d) *Family living standards (0–10 years)*: The quality of family living standards was assessed at annual intervals from age 1–10 years on the basis of interviewer ratings made on a five-point scale from very good to very poor. These ratings were averaged over the 10-year period to provide a global measure of the family's averaged standard of living over this period.

Measures of family functioning

(a) *Changes of parents (0–15 years)*: as part of the study detailed information was obtained at annual intervals from birth to age 15 years on any changes in family composition. An index of family instability during childhood was constructed on the basis of a count of the total number of changes of parents experienced by the child up to age 15 years. (b) *Parental attachment (15 years)*: the quality of parental attachments during adolescence was assessed at age 15 years using the Armsden & Greenberg [29] Parental Attachment Scale. The reliability of this

scale, assessed using coefficient alpha, was 0.87. (c) *Parental history of depression/anxiety (15 years)*: when sample members were aged 15, parents were questioned about their history of depression or anxiety problems: 29.9% of the sample had at least one parent who reported problems of depression or anxiety. (d) *Parental criminality (15 years)*: when sample members were aged 15, parents were questioned about their history of involvement in criminal offending: 13.3% of the sample had at least one parent who reported a history of criminality. (e) *Parental alcohol problems (15 years)*: when sample members were aged 15, parents were questioned about their history of alcoholism or problems with alcohol: 12.1% of the sample had at least one parent who reported alcohol problems. (f) *Parental illicit drug use (11 years)*: when sample members were aged 11 years, parents were questioned about their use of cannabis or other illicit drugs: 24.9% of the sample had at least one parent with a history of illicit drug use.

Measures of child abuse

(a) *Childhood sexual abuse (0–16 years)*: at ages 18 and 21 years sample members were questioned concerning their experience of childhood sexual abuse prior to age 16 years, and the nature/context of any episodes of abuse. Using these data, a four-level classification of the severity of abuse experience was constructed based on the worst episode of abuse reported at either age [30]. This classification was: no sexual abuse (86.0% of the sample); non-contact sexual abuse only (2.7%); contact sexual abuse not involving attempted or completed intercourse (5.1%); attempted or completed intercourse (6.2%). (b) *Childhood physical abuse (0–16 years)*: the extent of childhood physical abuse was assessed on the basis of the young person's reports of the extent of parental use of physical punishment during their childhood (prior to age 16 years), also obtained when sample members were aged 18 years and 21 years. The extent of physical punishment was coded on a four-point scale based on the highest level of physical punishment reported at either age [30]: parents never used physical punishment (4.5% of the sample); parents rarely used physical punishment (78.2%); at least one parent regularly used physical punishment (11.3%); at least one parent used physical punishment too often or too severely (6.0%).

Measures of individual characteristics

(a) *Gender*. (b) *Child neuroticism (14 years)*: this was assessed using a short-form version of the neuroticism scale of the Eysenck Personality Inventory [31] administered when sample members were aged 14 years. The reliability of this scale, assessed using coefficient alpha, was 0.80. (c) *Novelty seeking (16 years)*: the extent of novelty seeking behaviours was assessed using the novelty seeking subscale of the Tridimensional Personality Inventory [32] administered when sample members were aged 16 years. The reliability of this scale, assessed using coefficient alpha, was 0.76. (d) *Self-esteem (15 years)*: a measure of self-esteem was obtained at age 15 years using the Coopersmith Self-Esteem Inventory [33]. The full scale score was used in the present analysis and this measure had reliability (alpha) of 0.76. (e) *Child IQ (8 years)*: when sample members were aged 8 years, children were assessed on the Revised Wechsler Intelligence Scale for Children [34]. The full scale score was used in the present analysis. The reliability of this scale, assessed using split half methods, was 0.93.

Statistical analysis

Associations between frequency of cannabis use and psychotic symptoms

The first stage of the analysis reports the bivariate associations between the extent of cannabis use over the age intervals 17–18, 20–21 and 24–25 years and rates of psychotic symptoms reported at ages 18, 21 and 25. The association between the level of cannabis use and the rate of psychotic symptoms in each year was assessed using a negative binomial regression model in which the rate of psychotic symptoms was modelled as a log-linear function of the level of cannabis use. The negative binomial model provides a useful alternative to Poisson regression for count data in the presence of overdispersion, that is where the variance of the outcome variable is greater than would be expected of a true Poisson [35]. In each case the significance of the association was assessed using the log likelihood ratio χ^2 statistic for the effect of cannabis use from the fitted model. Tests were conducted using both linear models and design variates to assess the impact of cannabis use. These tests showed that, in all cases, the linear model provided the best fit to the observed data.

Covariate adjustment models

To adjust the associations between cannabis use and psychotic symptoms for confounding factors, a series of covariate adjustment models were fitted to the joint data over the three measurement periods. These models were as follows.

Model 1: the population averaged model. In this model the rate of psychotic symptoms at each time was modelled as a log-linear function of (a) the level of cannabis use in the

past year, (b) the set of observed fixed covariates described above and (c) the set of observed time-dynamic covariates described above. The kernel of this model was a Poisson regression model of the form:

$$\text{Log}\,(Yit) = B0 + B1\,Xit + \Sigma\,Bj\,Zj + \Sigma Bk\,Zkt$$

where Yit was the rate of psychotic symptoms for the *i*th participant at time *t*, X*it* was the corresponding measure of cannabis use at time *t*, Zj were the set of observed fixed covariates and Zkt the set of observed time-dynamic covariates. In this model, the coefficient B1 represents the effect of cannabis use on the rate of psychotic symptoms after adjustment for covariates. This coefficient gives an estimate of the averaged effect of cannabis use on psychotic symptoms after adjustment for covariates obtained by pooling observations over the three measurement periods. To take account of the correlations between repeated measures for the same participant over time the model also assumed an unstructured covariance matrix of the model disturbances over time.

Model 2: the random effects model. This model also adjusted the pooled association between frequency of cannabis use and psychotic symptoms for observed fixed and time-dynamic covariates. However, the model differed from Model 1 in that it also permitted an individual specific intercept term. The general form of this model was:

$$\text{Log}\,(Yit) = \alpha i + B1\,Xit + \Sigma\,Bj\,Zj + \Sigma Bk\,Zkt$$

where αi was the individual specific intercept and all other variables were as defined above. The random effects model assumes that the individual intercept terms are independent of each other and are uncorrelated with the other predictors in the equation [36].

Model 3: the conditional fixed effects model. The general form of this model was:

$$\text{Log}\,(Yit) = \alpha i + B1\,Xit + \Sigma Bk\,Zkt$$

In this model the ai are individual specific terms that are assumed to reflect the effects of all fixed sources of variation in the outcome Y*it*. These effects are assumed to be constant over time and may be correlated with other predictors in the model. The major advantage of the fixed effects model is that it can adjust for all sources of fixed covariate effects, including non-observed fixed confounders [37]. Thus, for example, the fixed effects model can adjust for such non-observed factors as fixed genetic factors that influence the risks of both cannabis use and psychotic symptoms.

More detailed accounts of the differences between these three models can be found in [35–37]. In the first instance, all three models were fitted to the data using Poisson regression methods. The analyses were then repeated using equivalent negative binomial regression models to account for overdispersion in the distribution of psychotic symptoms. Both sets of analyses produced the same conclusions, and the negative binomial results are reported in the paper. All models were fitted using Stata 6.0 [38].

From the fitted models, estimates of the adjusted incidence rate ratios (IRRs) of psychotic symptoms for varying levels of cannabis use were calculated relative to non-users of cannabis. For a given model, the adjusted IRR for a one-level increase in the frequency of cannabis use was given by e^{B1}, where B1 was the regression coefficient associated with cannabis use in the fitted model and e is the base of natural logarithms.

Structural equation modelling

Although the covariate adjustment models above address sources of confounding, these models do not provide tests of the direction of causality (if any) between cannabis use and psychotic symptoms. To explore this issue, a series of structural equation models were fitted to the data. These models are depicted in Figs 1 and 2.

The model in Fig. 1 assumes that: (a) the observed measures of cannabis use (Ct, $t = 1,2,3$) over the three time periods are linked by an autoregressive structure in which past cannabis use predicts future cannabis use; (b) the observed measures of psychotic symptoms (Pt, $t = 1,2,3$) are also linked by a similar autoregressive structure in which past symptoms predict future symptoms; (c) within time periods cannabis use and psychotic symptoms are potentially reciprocally related so that (i) current cannabis use may influence current psychotic symptoms and (ii) current psychotic symptoms may influence current cannabis use. These reciprocal effects are assumed to be constant over time. The model specification is:

Model equations

$$C3 = B1\,P3 + B3\,C2 + B5\,C1 + \nu 3 \qquad P3 = B2\,C3 + B6\,P2 + B8\,P1 + \tau 3$$
$$C2 = B1\,P2 + B4\,C1 + \nu 2 \qquad P2 = B2\,C2 + B7\,P1 + \tau 2$$
$$C1 = B1\,P1 + \nu 1 \qquad P1 = B2\,C1 + \tau 1$$

Model assumptions

$$\text{Cov}\,(\nu r, \tau s) = \text{Cov}\,(\nu r, \nu s) = \text{Cov}\,(\tau r, \tau s) = 0 \text{ for } r \neq s$$
$$\text{Cov}\,(Cr, \nu s) = \text{Cov}\,(Pr, \nu s) = 0 \text{ for } r < s$$
$$\text{Cov}\,(Cr, \tau s) = \text{Cov}\,(Pr, \tau s) = 0 \text{ for } r < s$$

In terms of assessing the direction of causality between cannabis use and psychotic symptoms, the values of the parameters B1, B2 may provide important information about both the size and direction of this influence.

A limitation of the autoregressive model in Fig. 1 is that this model does not take into account common con-

founding factors that may influence both cannabis use and psychotic symptoms. This issue is addressed in the model in Fig. 2 which includes fixed effects factors to take into account: (i) fixed factors that influence cannabis use and (ii) fixed factors that influence psychotic symptoms. Specifically, the model assumes that: (a) the observed measures of cannabis use (Ct) are influenced by fixed sources of variance (C) that are constant over time and time-dynamic sources of variation (Ut); (b) the observed measures of psychotic symptoms (Pt) are also influenced by fixed sources of variation (P) that are constant over time and time-dynamic sources of variation (Wt); (c) the fixed factors C and P are permitted to be correlated; (d) the time-dynamic components of cannabis use (Ut) and psychotic symptoms (Wt) are linked by autoregressive processes in which past cannabis use predicts future cannabis use and past psychotic symptoms predict future psychotic symptoms, respectively; (e) the time dynamic components of cannabis use and psychotic symptoms are reciprocally related so that current Ut influences current Wt and vice versa. These reciprocal effects are assumed to be constant over time. The specification for this model as follows:

Model equations

$Ct = C + Ut\ (t = 1, 2, 3)$ $\quad Pt = P + Wt\ (t = 1, 2, 3)$

$U3 = B1\ W3 + B3\ U2 + \nu 3$ $\quad W3 = B2\ U3 + B5\ W2 + \tau 3$

$U2 = B1\ W2 + B4\ U1 + \nu 2$ $\quad W2 = B\ U2 + B6\ W1 + \tau 2$

$U1 = B1\ W1 + \nu 1$ $\quad W1 = B2\ U1 + \tau 1$

Model assumptions

$Cov\ (C, Ut) = Cov\ (C, Wt) = Cov\ (C, \nu t) = Cov\ (C, \tau t) = 0\ (t = 1, 2, 3)$

$Cov\ (P, Ut) = Cov\ (P, Wt) = Cov\ (P, \nu t) = Cov\ (P, \tau t) = 0\ (t = 1, 2, 3)$

$Cov\ (\nu r, \tau s) = Cov\ (\nu r, \nu s) = Cov\ (\tau r, \tau s) = 0$ for r^1 s

$Cov\ (Cr, \nu s) = Cov\ (Cr, \tau s) = Cov\ (Pr, \nu s) = Cov\ (Pr, \tau s) = 0$ for $r < s$

$Cov\ (Ur, \nu s) = Cov\ (Ur, \tau s) = Cov\ (Wr, \nu s) = Cov\ (Wr, \tau s) = 0$ for $r < s$

The advantage of the model specification in Fig. 2 is that it estimates the pathways between cannabis use and psychotic symptoms, taking into account non-observed fixed factors associated with these measures.

The models depicted in Figs 1 and 2 were fitted to the observed measures of cannabis use and psychotic symptoms at age 18, 21 and 25 years. As the observed measures were markedly non-normally distributed the models were fitted to the covariance matrix of the observed data using the method of weighted least squares. All models were fitted using LISREL 8 [39]. Model goodness of fit was assessed on the basis of a number of indices including: (a) the log-likelihood ratio χ^2 statistic; (b) the root mean squared error of approximation (RMSEA). Values of RMSEA less than 0.05 are assumed to be indicative of a well-fitting model; (c) the standardized root mean squared residual correlation (RMSR) between the observed measures. Values of RMSR close to zero indicate a well-fitting model. (d) The Comparative Fit Index (CFI). This index varies between 0 and 1 with values close to 1 indicating a well-fitting model [39].

Missing data and sample bias

As noted above, the analysis is based on the sample of 1055 participants for whom data on cannabis use and

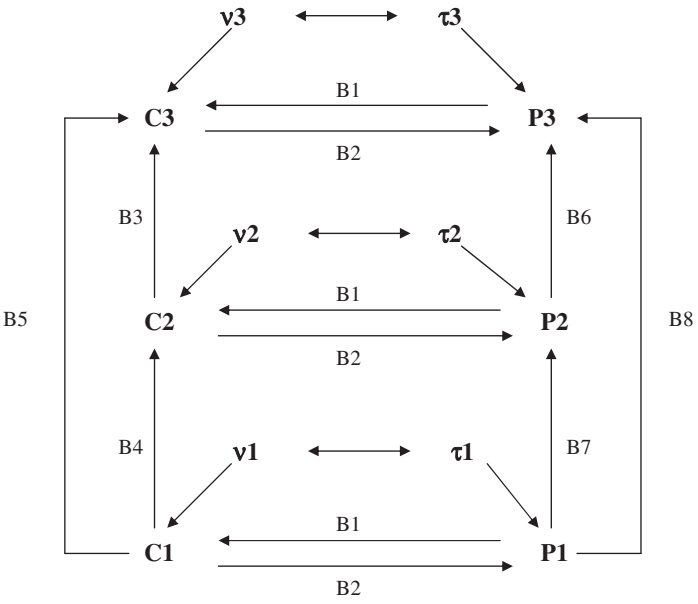

Figure 1 Autoregressive model of cannabis use and psychotic symptoms with reciprocal paths between cannabis use and psychotic symptoms. Ct = cannabis use at time *t*; Pt = psychotic symptoms at time *t*; νt = disturbance term for Ct; τt = disturbance term for Pt

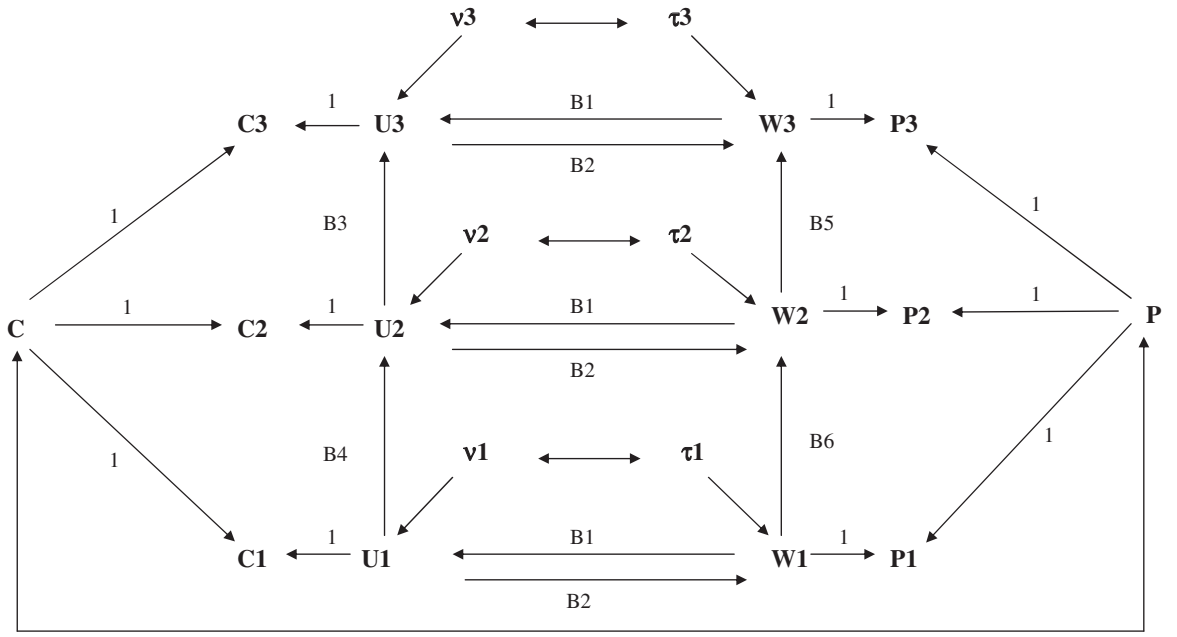

Figure 2 Auroregressive model of cannabis use and psychotic symptoms incorporating fixed effects and reciprocal paths between dynamic components of canabis use and psychotic symptoms. Ct = cannabis use at time *t*; Pt = psychotic symptoms at time *t*; C = fixed effects component of Ct; P = fixed effects component of Pt; Ut = time dynamic component of Ct; Wt = time dynamic component of Pt; νt = disturbance term for Ut; τt = disturbance term for Wt

psychotic symptoms were available on at least one occasion from 18, 21 and 25 years. However, as not all participants were assessed at all ages the observed sample numbers vary between age 18 ($n = 1025$), age 21 ($n = 1011$) and age 25 ($n = 1003$). These samples represented between 79% and 81% of the initial cohort of 1265 participants. In addition, as a result of missing data on some covariates the sample number included in the covariate adjustment analyses was reduced to approximately 900.

To examine the implications of sample attrition and missing data for study conclusions a series of additional analyses were undertaken. First, regression imputation methods were used to impute estimates for the missing data on covariate factors, and the covariate adjustment analyses were repeated with the missing data replaced by their imputed values. The regression imputation was conducted using the impute procedure of Stata 6.0 [38]. Secondly, to adjust for possible sample selection bias resulting from sample attrition, the methods described by Carlin *et al.* [40] were used. These methods involved a two-stage analysis process. In the first stage of the analysis, a sample selection model was constructed by using data gathered at birth to predict participation at each age. This analysis showed that there were statistically significant ($P < 0.05$) tendencies for the obtained sample at each age to under-represent children from more socially disadvantaged backgrounds (low parental education, low socio-economic status, single-parent family). On the basis of the fitted selection models, the sample was then poststratified into a series of groups and the probability of study participation estimated for each group at each age.

In the second stage of the analysis the data were reanalysed by fitting a negative binomial regression model to the full data with the observations for each individual weighted by the inverse of the probability of study participation at each age to adjust for sample selection bias. All analyses produced essentially identical conclusions to the findings reported here, suggesting that the effects of missing data and possible sample selection bias on the results were likely to be minimal.

RESULTS

Associations between cannabis use and rates of psychotic symptoms at 18, 21 and 25 years

Table 1 shows the relationship between reported rates of cannabis use in the past 12 months at ages 18, 21 and 25 years, and self-reported psychotic symptoms at these ages. Each comparison is tested for statistical significance using the log likelihood ratio χ^2 statistic derived from a negative binomial regression model. The analysis shows that at all ages there were clear and highly statistically

significant ($P < 0.0001$) trends for increasing use of cannabis to be associated with increasing rates of psychotic symptoms: young people who were daily users of cannabis had rates of psychotic symptoms that were between 2.3 and 3.3 times higher than the rates for those who did not use cannabis.

Adjustments for covariate factors

As explained in the Methods, the associations between cannabis use and psychotic symptoms were adjusted for observed covariates using three approaches to covariate adjustment: (a) a population averaged model using observed fixed and time dynamic covariates; (b) a random effects model using observed fixed and time-dynamic covariates; and (c) a fixed effects model that took into account both non-observed fixed factors and observed time dynamic covariates. The results of these analyses are given in Table 2, which shows the incidence rate ratios (IRRs) of psychotic symptoms and corresponding 95% confidence intervals associated with each model after adjustment for covariates. In each case the IRRs show the rate of psychotic symptoms for a given level of cannabis use relative to non-users. All models yield highly consistent estimates that suggest that those who used cannabis daily had rates of psychotic symptoms that were in the region of 1.6–1.8 times higher than those who did not use cannabis. Furthermore, the findings suggest that the adjustments for observed covariates in Models 1 and 2 produce conclusions that are consistent with the adjustments for non-observed covariates using the fixed effects model.

Results from reciprocal causes models

The findings in Table 2 are consistent with the view that cannabis use and psychotic symptoms may be linked by a cause-and-effect model. However, the analysis does not establish that this association is one in which increasing frequency of cannabis use leads to increased psychotic symptoms. To address this issue, the data were analysed using the reciprocal cause structural equation models described in the Methods. These models include the autoregressive model shown in Fig. 1 and the autoregressive model including fixed effects factors shown in Fig. 2. The key findings of this analysis are summarized in Table 3 which shows: (a) estimates of the fitted model

Table 1 Mean psychotic symptoms (number of subjects) by frequency of cannabis use (past 12 months) at 18, 21 and 25 years.

	Frequency of cannabis use (past 12 months)					
Age (years)	*Never*	*Less than monthly*	*At least monthly*	*At least weekly*	*Daily*	*P*
18	0.64 (598)	0.95 (242)	1.07 (82)	1.93 (70)	1.64 (33)	<0.0001
21	0.69 (538)	1.00 (215)	1.14 (100)	1.48 (94)	1.61 (64)	<0.0001
25	0.60 (559)	0.89 (232)	0.93 (76)	1.15 (81)	1.95(55)	<0.0001

Table 2 Estimated incidence rate ratios (95% CI) of psychotic symptoms by level of cannabis use after adjustment for covariates.

Covariate adjustment model	*Frequency of cannabis use (past 12 months)*					
	Never	*Less than monthly*	*At least monthly*	*At least weekly*	*Daily*	*P*
Model 1: population averaged (observed fixed[1] and time dynamic[2] covariates)						
IRR	1 (95% CI)	1.12 (1.05–1.20)	1.25 (1.09–1.43)	1.40 (1.14–1.71)	1.56 (1.20–2.04)	<0.001
Model 2: random effects (observed fixed[1] and time dynamic[2] covariates)						
IRR	1 (95% CI)	1.12 (1.05–1.19)	1.24 (1.10–1.41)	1.39 (1.15–1.68)	1.55 (1.21–1.99)	<0.001
Model 3: fixed effects (non-observed fixed and observed[2] time dynamic covariates)						
IRR	1 (95% CI)	1.15 (1.06–1.25)	1.33 (1.13–1.56)	1.53 (1.20–1.95)	1.77 (1.28–2.44)	<0.001

[1]Observed fixed covariates included: gender; parental education; family socio-economic status; family living standards; changes of parents; parental alcohol problems; parental illicit drug use; parental depression/anxiety; parental criminality; childhood sexual abuse; childhood physical abuse; neuroticism; novelty seeking; self-esteem; parental attachment; child IQ. [2]Observed time dynamic covariates included: prior psychotic symptoms; prior frequency of cannabis use; concurrent and prior mental disorders (major depression, anxiety disorders, alcohol dependence, nicotine dependence, illicit drug dependence, conduct disorder/aspd); adverse life events; deviant peer affiliations.

parameters and standard errors for the effects of cannabis use on psychotic symptoms and the effects of psychotic symptoms on the frequency of cannabis use; (b) measures of model fit including the log likelihood ratio χ^2 test statistic, the (RMSEA), the standardized root mean squared residual correlation (SRMR) and the comparative fit index (CFI). The results of the structural equation models suggest the following conclusions:

1 For both models, cannabis use had a positive and significant effect ($P < 0.001$) on psychotic symptoms, implying that increasing cannabis use was associated with increased symptom levels.
2 For both models, the effect of psychotic symptoms on cannabis use was negative and, for Model 2, statistically non-significant. These results imply that it was unlikely that the development of psychotic symptoms led to increased use of cannabis and that, if anything, the development of these symptoms may have inhibited rather than encouraged cannabis use.
3 Both models proved to be well fitting on the basis of a range of goodness of fit measures.

Collectively, the results in Tables 2 and 3 are consistent with two major conclusions. First, the use of cannabis and rates of psychotic symptoms were related to each other, independently of observed/non-observed fixed covariates and observed time dynamic factors (Table 2). Secondly, the results of structural equation modelling suggest that the direction of causation is that the use of cannabis leads to increases in levels of psychotic symptoms rather than psychotic symptoms increasing the use of cannabis. Indeed, there is a suggestion from the model results that increases in psychotic symptoms may inhibit the use of cannabis.

DISCUSSION

This analysis has used data gathered over the course of a 25-year longitudinal study to address two issues regarding the linkages between the use of cannabis and psychotic symptoms. The first issue concerned the extent to which the association between cannabis use and psychotic symptoms reflected uncontrolled confounding factors. The second issue addressed the direction of causality (if any) between cannabis use and psychotic symptoms. The findings of these analyses are reviewed below.

The effects of confounding factors

One of the more controversial issues regarding linkages between cannabis use and psychosis/psychotic symptoms has concerned the extent to which these linkages reflect uncontrolled residual confounding [15]. In this paper we have attempted to address this problem by adjusting these associations using two approaches to covariate control. In the first approach we controlled for observed confounders using extensive prospectively collected covariate data. In the second approach we used fixed effects regression to control for non-observed fixed sources of confounding. Both methods of adjustment gave similar results and suggested the presence of a dose–response relationship between the frequency of cannabis uses and rates of psychotic symptoms. It was estimated that daily users of cannabis had rates of these symptoms that were 1.6–1.8 times higher than non-users of cannabis even after both observed and non-observed sources of confounding were taken into account.

These results add to a growing body of evidence that now suggests that the linkages between cannabis use and psychotic symptoms are likely to be causal and are unlikely to be due to sources of uncontrolled residual confounding. None the less, the possibility of residual confounding cannot be dismissed entirely because although the regression models used in this analysis controlled for both observed and non-observed fixed factors, the possibility of confounding by (non-fixed) time-dynamic factors remains. A further issue concerns the assessment of psychotic symptoms. In this study we have used a scale measure based on a count of symptoms. However, it could be suggested that this measure differs

Table 3 Estimated reciprocal effects of frequency of cannabis use and psychotic symptoms for alternative structural equation models.

	Effect of cannabis use on psychotic symptoms		*Effect of psychotic symptoms on cannabis use*	
Model	*B (SE)*	*P*	*B (SE)*	*P*
Model 1: autoregressive model on observed variables				
	0.154 (.044)	<0.001	– 0.094 (.047)	<0.05
Model 2: autoregressive model incorporating non-observed fixed effects				
	0.352 (.087)	<0.001	– 0.045 (.043)	>0.25

Goodness of fit indices: (a) for model 1, LR χ^2 (4) = 7.6, $P > 0.10$; RMSEA = 0.03, $P > 0.80$; SRMR = 0.029; CFI = 0.998. (b) For model 2, LR χ^2 (5) = 4.00, $P > 0.50$; RMSEA = 0.00, $P > 0.98$; SRMR = 0.017; CFI = 1.00.

from diagnostic classification and also may not disclose all aspects of psychosis. While measurement issues are a potential threat to validity in studies of cannabis and psychosis, this threat does not appear to be large. As recent reviews [1–3] have shown, authors using range of measures including diagnostic classifications and scale dimensions have been able to show linkages between the use of cannabis and rates of psychosis/psychotic symptoms. Despite these caveats we believe that the weight of the evidence is now firmly in favour of the view that cannabis use and psychosis/psychotic symptoms are likely to be causally related.

Direction of causality

The demonstration that cannabis use and psychotic symptoms remain associated even following control for confounding suggests a causal linkage, but does not establish the direction of causality. There are potentially two causal pathways by which cannabis use and psychosis may be linked. First cannabis use may lead (via biochemical changes in the brain) to increased rates of psychotic symptoms amongst susceptible users. Alternatively, those prone to psychosis or psychotic symptoms may be more prone to use cannabis as a consequence of their condition and perhaps as an attempt at self-medication [41,42]. Resolving this issue is clearly critical to understanding the causal role that cannabis use may play in psychosis. To address this issue we have employed methods of structural equation modelling that permit estimation of reciprocal causal pathways. Two models were fitted, with the first using a relatively simple autoregressive structure to identify model parameters and the second incorporating fixed effects models for cannabis use and psychotic symptoms. Both models led to similar conclusions about the possible causal linkages between cannabis use and psychotic symptoms. First, there was clear evidence to suggest that increasing use of cannabis was associated with statistically significant increases in the risks of psychotic symptoms. Secondly, increasing psychotic symptoms were not positively associated with increased rates of cannabis use and indeed the fitted autoregressive model suggested that the association between psychosis and cannabis use may be negative, so that increasing psychotic symptoms were associated with a decline in the use of cannabis. The weight of the evidence from the SEM approach clearly suggests the presence of a causal process in which increasing use of cannabis is associated with increasing rates of psychotic symptoms.

Of course, these conclusions rest upon some of the relatively strong assumptions (see Methods) required to identify these models, but it is important to note that these assumptions did not favour finding a particular causal pathway between cannabis use and psychotic symptoms.

Does cannabis use cause psychosis?

Finally, the present study needs to be seen in the context of a wider literature that has explored the issue of cannabis use and psychosis. This literature is beginning to provide the foundations of a coherent picture that supports the view that cannabis use may contribute to psychosis or psychotic symptoms in individuals vulnerable to these conditions. This evidence includes:

1. The growing epidemiological evidence (including the present study) that suggests evidence of dose–response relationships between the extent of cannabis use and subsequent psychosis/psychotic symptoms even following control for sources of confounding and possible reverse causality [4–7].
2. Evidence from clinical studies suggesting that cannabis use is associated with an increased relapse rate in individuals with schizophrenia [43,44].
3. Growing neuropsychological evidence on the multiple effects of cannabis on the brain and brain biochemistry [12,13].
4. Evidence from laboratory-based studies suggesting that the acute effects of cannabis intoxication may create psychotic-like symptoms and may be used as a 'model' psychosis [8,11].

Although each of these lines of evidence is subject to uncertainty and debate, the weight of the evidence clearly suggests that the use of cannabis (and particularly the heavy use of cannabis) may alter underlying brain chemistry and precipitate the onset of psychosis/psychotic symptoms in vulnerable individuals. The present study adds to this evidence by showing: (a) it is unlikely (although not impossible) that the association between cannabis use and psychotic symptoms in a population sample was due to confounding factors, and (b) the predominant direction of causality is likely to involve a path from cannabis use to psychotic symptoms rather than a path from psychotic symptoms to cannabis use.

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