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Fergusson DM, Boden JM, Horwood LJ. Cannabis use and other illicit drug use: Testing the cannabis gateway hypothesis. *Addiction*, 2006; 101: 556-569.

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**Cannabis use and other illicit drug use: Testing the cannabis
gateway hypothesis**

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Acknowledgements: This research was funded by grants from the Health Research Council of New Zealand, the National Child Health Research Foundation, the Canterbury Medical Research Foundation and the New Zealand Lottery Grants Board.

Abstract

Aim: To examine the associations between the frequency of cannabis use and the use of other illicit drugs.

Design: A 25-year longitudinal study of the health, development, and adjustment of a birth cohort of 1,265 New Zealand children.

Measurements: Annual assessments of the frequency of cannabis use were obtained for the period 14-25 years, together with measures of the use of other illicit drugs from the same time period.

Findings: The frequency of cannabis use was significantly associated with the use of other illicit drugs, other illicit drug abuse/dependence, and the use of a diversity of other drugs. This association was found to be particularly strong during adolescence but declined rapidly as age increased. Statistical control for confounding by both fixed and time dynamic factors using random- and fixed-effects regression models reduced the strength of association between frequency of cannabis use and other illicit drug use, but a strong association between frequency of cannabis use and other illicit drug use remained even after control for non-observed and time-dynamic sources of confounding.

Conclusions: Regular or heavy cannabis use was associated with an increased risk of using other illicit drugs, abusing or becoming dependent upon other illicit drugs, and using a wider variety of other illicit drugs. The risks of use, abuse/dependence, and use of a diversity of other drugs declined with increasing age. The findings may support a general causal model such as the cannabis gateway hypothesis, but the actual causal mechanisms underlying such a gateway, and the extent to which these causal mechanisms are direct or indirect, remain unclear.

Keywords: cannabis, illicit drug use, gateway, longitudinal study, fixed-effects models

Cannabis use and other illicit drug use: testing the cannabis gateway hypothesis

In recent decades there has been growing interest in the effects of cannabis use on mental health and adjustment (e.g. 1, 2-8). One aspect of this concern has been the extent to which cannabis acts as a “gateway drug” which leads to the use of other drugs such as cocaine, methamphetamine, and heroin at a later point in time (e.g. 9, 10-16). The gateway hypothesis implicitly assumes a causal chain sequence in which a) cannabis is used prior to the onset of other illicit drugs and b) the use of cannabis increases the likelihood of using other illicit drugs. There have been three lines of evidence that support the view that the links between cannabis use and other illicit drug use may be causal.

The first kind of evidence for the gateway theory of cannabis use is the observation of a temporal sequence in the use of cannabis and other illicit drugs. There is strong and consistent evidence that the use of cannabis almost invariably precedes the use of other illicit drugs. For example, Kandel and Yamaguchi (17), using data from a national cross-sectional sample, found that although most cannabis users did not proceed to use cocaine and heroin, 90% of cocaine users had used cannabis prior to using cocaine. Golub and Johnson (18), in a study of serious drug abusers in New York City, found that a large proportion of their sample (91%) began their illicit drug use with cannabis. Similar findings were reported by Kandel, Yamaguchi, and Chen (19), who found that between 86% and 90% of persons using both cannabis and other illicit drugs used cannabis prior to the use of other illicit drugs. A strong temporal sequence was also found in a study of the present cohort by Fergusson and Horwood (20), who reported that of those individuals who used both cannabis and other illicit drugs, fewer than 1% used other illicit drugs prior to using cannabis.

The second kind of evidence used to support the gateway theory of cannabis use is the strength of association between cannabis use and other illicit drug use. For example, one US study found that users of cannabis were 85 times more likely than non-users to use other illicit drugs (21). Kandel (22) reported that only 7% of American youths who had never used cannabis reported using

other illicit drugs, whereas 33% of occasional cannabis users and 84% of daily cannabis users reported using other illicit drugs. Fergusson and Horwood (20) reported that those who had used cannabis at least weekly were 59 times more likely to engage in other illicit drug use. Lynskey and colleagues (23), using a discordant twin design, found that those who had used cannabis were 2.1 to 5.2 times more likely to use other illicit drugs.

A critical issue in evaluating the gateway hypothesis concerns the extent to which the associations between cannabis use and other illicit drug use can be explained by third or confounding factors. There have been two models proposed to explain the linkage between cannabis and other illicit drugs. The first model, deriving from problem behavior theory (24-26), assumes that the association arises because of common factors that predispose young people to use both cannabis and other illicit drugs. A number of early studies in this area claimed that it was possible to explain the association between cannabis and other illicit drug use using a common factors model (24, 27, 28). This view was also supported by a simulation model reported by Morral and colleagues (29), who conducted a Monte-Carlo simulation using a common factors model. This analysis showed that an underlying common factor (drug use propensity) could account for the data on the sequencing of drug use and the correlations between cannabis use and other illicit drug use, provided that opportunities to use cannabis were more plentiful than opportunities to use other illicit drugs.

However, other studies employing often extensive control for confounding factors have reported that associations between cannabis use and other illicit drug use cannot be explained by confounding factors (20, 30-32). A potential criticism of much of this research is that studies had only controlled observed covariates and that any association between cannabis use and other illicit drug use could be attributed to residual confounding (29). This raises important issues about methods for controlling both observed and non-observed confounding.

Although it is commonly believed that epidemiological studies can only control observed factors, this is not strictly true. There are at least two approaches by which non-observed sources of

genetic and environmental confounding may be controlled using a correlational design. The first approach is via the discordant twin design. In this design monozygotic twins who are discordant for cannabis use would be compared on their use of other illicit drugs. Since monozygotic twins share common genes and a common environment this comparison could account for these non-observed factors. This approach was used by Lynskey and colleagues (23) in a study of twin pairs. The study concluded that the use of cannabis was associated with a 2.1 to 5.2 times higher risk of subsequent use of illicit drugs even after common genes and environment were taken into account.

The second approach which is suitable for samples of singletons is provided by the fixed effects regression model. This model makes it possible to take into account non-observed genetic and environmental factors that have a fixed effect on the association between cannabis use and other illicit drug use. The logic of the fixed effects model can be illustrated by the following example in which interest centers on the relationship between an exposure variable X and a continuous and normally distributed outcome Y , which are both observed at repeated time periods. Let X_{it} , Y_{it} denote the scores on x and y of the i th individual at time t . Assume that the model linking Y_{it} and X_{it} is given by

$$Y_{it} = B_0 + B_1 X_{it} + U_i + E_{it} \quad (1)$$

where U_i represents nonobserved systematic factors that influence the outcome Y for subject i and E_{it} is a random error term. The non-observed variable U_i represents all fixed (i.e. time invariant) factors that influence the score Y_{it} . This variable thus represents all potential fixed sources of confounding that could influence the relationship between X_{it} and Y_{it} . If U_i were an observed variable it would be a straightforward matter to fit the model in Equation 1 taking into account the sources of confounding represented by U_i . Subject to the model in Equation 1 being correctly specified, this would lead to the causal effect B_1 of X_{it} on Y_{it} being correctly estimated. The difficulty that arises is that U_i is not observed.

However, it proves possible to estimate the parameter B_1 in the following way. First sum Equation 1 over the time periods t ($t = 1 \dots n$) and divide both sides of the equation by n . This operation yields:

$$y_i = B_0 + B_1 x_i + U_i + e_i \quad (2)$$

where y_i is the mean value of Y_{it} over the n time periods, x_i is the corresponding mean value of X_{it} , and e_i is the mean value of the disturbance E_{it} . Subtracting Equation 2 from Equation 1 gives

$$(Y_{it} - y_i) = B_1(X_{it} - x_i) + (E_{it} - e_i) \quad (3)$$

The important feature of Equation 3 is that it provides a means of estimating the parameter of interest B_1 in a way that takes into account the non-observed fixed sources of confounding represented by the variable U_i (this follows since Equation 3 gives an estimate of B_1 but the solution of this equation does not depend on knowledge of the value of U_i).

At this point it is useful to clarify the meaning of the fixed effect factor U_i and to consider the types of non-observed variables that might contribute to the fixed effects term. Such factors will be characterized by two general features: a) the factor will be a fixed feature of the individual or his/her social context; and b) the factor will be related to later outcomes Y_{it} by a main effects model in which the effects of the factor are constant across all observation periods.

In the context of research into cannabis use and later other illicit drug use, factors that may potentially be included in the fixed effects term are all individual, family, social, and related factors that are fixed at the point of adolescence and which have a fixed effect on later cannabis use and illicit drug use. It is clear from the above that control for fixed effects does not control all confounding processes that may affect the association between Y_{it} and X_{it} . Specifically, the model does not control for: a) fixed confounding factors whose effects on cannabis use and other illicit drug use vary with age; b) fixed confounding factors that combine interactively with X_{it} to influence Y_{it} ; and c) time dynamic covariate factors.

As noted above, a limitation of the fixed effects model in Equation 3 is that it does not take into account covariate factors that vary with time. However, this issue may be addressed by extending the model to include observed time dynamic variables

$$(Y_{it}-y_i) = B_1(X_{it} - x_i) + \sum B_j(Z_{ijt} - z_{ij}) + (E_{it}-e_i) \quad (4)$$

where the variables Z_{ijt} are covariate measures that may vary with time and z_{ij} is the mean of the j th covariate Z_{ijt} over the n time periods.

Although the fixed effects model described in Equation 3 has been used widely in economic applications (e.g. 33), it has been less often applied in epidemiological and public health research. One possible reason for this is that often such research uses either dichotomous outcome measures or rate information that is non-normally distributed and ill-suited to ordinary least-squares regression. In recent years the fixed effects model has been generalized to provide estimates for both dichotomous outcome measures and count data through the use of conditional fixed effects logistic and Poisson regression models (34, 35). Although the methods of estimation for these models differ from the methods of the linear regression model they produce estimates of the effects of an exposure variable X_{it} on an outcome variable Y_{it} adjusted for non-observed sources of confounding U_i .

Against this background the aims of the present investigation were to test the cannabis gateway hypothesis using data gathered in the course of a 25-year longitudinal study of a birth cohort of over 1,000 New Zealand young adults. The aims of this study were:

1. To document the temporal sequence linking cannabis use to other illicit drug use over the period 14-25 years.
2. To estimate the size of associations between cannabis use and other illicit drug use after correction for observed sources of confounding.
3. To determine the extent to which the frequency of cannabis use was associated with later other illicit drug use after controlling for non-observed fixed effects, using the general model developed in Equation 4.

4. To examine the extent to which the trends evident for cannabis use also applied to measures of other illicit drug abuse/dependence and diversity of drug use.

Method

The data were gathered as part of the Christchurch Health and Development Study (CHDS). The CHDS is a longitudinal study of a birth cohort of 1,265 children born in the Christchurch (New Zealand) urban region in mid-1977. The cohort has been studied at birth, 4 months, 1 year and at annual intervals to age 16 years, and again at ages 18, 21, and 25. The study has collected information from a variety of sources including: parental interviews, teacher reports, self-reports, psychometric assessments, medical, and other record data. An overview of the study design, methodology, and major findings can be found in Fergusson, Horwood, Shannon, and Lawton (36) and Fergusson and Horwood (37). The present analysis used the following measures:

Cannabis use. At ages 15, 16, 18, 21, and 25, cohort members were questioned about their use of cannabis since the previous assessment. The data collection provided an account of the individual's reported frequency of cannabis use for each year from age 14-15 to age 24-25. For the purposes of this analysis, the annual frequency data were classified into a series of class intervals as follows: did not use cannabis; used less than monthly on average (1-11 times); used at least monthly on average (12-50 times); used at least weekly on average (more than 50 times). In the present analysis, this information was used to provide estimates of the frequency of cannabis use in each year to examine the associations between frequency of cannabis use and a) the onset of other illicit drug use; b) other illicit drug abuse/dependence; and c) the diversity of other illicit drugs used; for each year from 14-15 to 24-25.

Outcome measures

Other illicit drug use. At ages 15, 16, 18, 21, and 25, cohort members were questioned about their use of illicit drugs other than cannabis since the previous assessment. As with the assessment of cannabis use, each assessment included questions about other illicit drug use for each year of the assessment period. The cohort members were questioned about their use of a range of illicit drugs, including solvents (glue, petrol, paint); stimulants (including methamphetamine); barbiturates; other prescription medications that were illicitly obtained; opiates, including both heroin and morphine; cocaine (in any form); hallucinogens including ecstasy, LSD, and PCP; and any other substances (primarily plant extracts) including mushrooms and datura. For the purposes of this analysis, participants were classified as having used other illicit drugs in a given year if they reported using any of the above classes of substances on at least one occasion.

Other illicit drug abuse/dependence. At each assessment from 15 years cohort members were questioned about symptoms of other illicit drug abuse and dependence using a series of questions based on DSM criteria (38, 39) for substance use disorders. At ages 15 and 16 years this questioning was based on custom-written survey items designed to assess DSM-III-R criteria for substance abuse/dependence, while at ages 18, 21, and 25, items derived from the Composite International Diagnostic Interview (CIDI: 40) were used to assess DSM-IV criteria for abuse/dependence. Cohort members meeting the diagnostic criteria for other illicit drug abuse/dependence in any given year were classified as other illicit drug abusing/dependent for that year.

Drug diversity. Questions regarding the use of other illicit drugs were also used to create a drug diversity outcome measure, representing the number of different other illicit drugs a participant used in any given year. For the purposes of this analysis, participants were classified as having used a particular class of substance in a given year if they reported using any drug within the

substance class on at least one occasion. These responses were then summed to generate a continuous drug diversity scores for each year from age 14-15 to age 24-25.

Confounding factors

The present investigation used two methods for controlling confounding factors. The first method was through the use of random-effects regression models that controlled for both observed, fixed confounding factors (for the period prior to age 15), and time-dynamic confounding factors that were measured during the period 14-25 years. The second method was through the use of fixed-effects regression models (see Introduction) that controlled for both non-observed fixed sources of confounding and time-dynamic confounding factors that were measured from ages 14-25. Thus the two sets of models shared the use of the same time-dynamic factors.

The random effects models, however, employed a series of observed covariate factors that were abstracted from the study data base and were selected on the basis that a) they were theoretically relevant predictors of cannabis use or other illicit drug use and b) they were known on the basis of prior analysis to be significantly associated with either cannabis use or other illicit drug use in the cohort. As far as possible these measures were assessed prior to age 15. However, in some cases the assessment involved the period up to age 16 years.

Measures of socio-economic background

Family socio-economic status at birth – Assessed at birth using the scale developed for New Zealand by Elley and Irving (41).

Maternal age – Recorded at birth.

Maternal education – Mother's highest educational attainment, recorded at birth.

Average family living standards (ages 0-10) – assessed via a global assessment of material living standards made by an interviewer during each year, and averaged across this period.

Family functioning

Changes of parents (age 15) – A measure reflecting the total number of parental changes occurring up to age 15 as a result of separation/divorce, reconciliation, fostering, remarriage, or death (42).

Parental attachment (age 14) – Assessed at age 14 using the parental attachment scale developed by Armsden and Greenberg (43), $\alpha = .91$.

Parental history of offending, alcohol abuse/dependence, and illicit drug use – Parental illicit drug use was assessed at age 11 (24.9% of the sample were thus classified), and at age 15 offending (12.4% of the sample) and alcohol abuse/dependence (11.9% of the sample) were assessed.

Child abuse

Childhood sexual abuse – Assessed at ages 18 and 21 for the period up to and including 15 years, spanning an array of abusive experiences, resulting in a 4-level classification of severity (44).

Parental use of physical punishment – Assessed at ages 18 and 21 for the period during childhood, resulting in a 4-level classification of the extent to which physical punishment was used (45).

*Individual characteristics and behavior**Gender*

Novelty-seeking (age 16) – Assessed using the novelty-seeking items from the Tridimensional Personality Questionnaire (46), $\alpha = .76$.

Neuroticism (age 14) – Assessed using the Neuroticism scale of the Eysenck Personality Inventory (47), $\alpha = .80$.

Self-esteem (age 15) – Assessed using the global scale of the Coopersmith (48) Self-Esteem Scale ($\alpha = .87$).

IQ – Assessed at ages 8 and 9 (and averaged across these ages) using the Revised Wechsler Intelligence Scale for Children (WISC-R: 49).

Grade Point Average ages 11-13 – Assessed via teacher reports of achievement in reading, written expression, spelling, and mathematics and averaged over these domains and age intervals.

Conduct problems age 14 – Assessed via parent and child reports of child behavior issues at age 14 using items from the Rutter et al (50) and Conners (51) behavior scales, and from the Diagnostic Interview Schedule for Children (DISC: 52), $\alpha = .90$.

Conduct and attention problems ages 7-9 – Assessed via parent and teacher reports of child behavior at ages 7, 8, and 9 using items from the Rutter et al (50) and Conners (51, 53) behavior scales, $\alpha = .97$ and $.93$, respectively.

Frequency of cigarette smoking age 14 – Assessed on a five-point scale ranging from non-smoker to daily smoker.

Frequency of alcohol use age 14 – Assessed via self-reported number of occasions of alcohol use over the previous 3 months.

School drop out – Those leaving school prior to the official school leaving age (16 years) were classified as having dropped out of school (4.6% of the sample).

Time dynamic covariate factors

Both the random- and fixed-effects models employed a set of time-dynamic covariate factors in order to determine the extent to which the associations between frequency of cannabis use and later other illicit drug use were due to social and personal issues occurring during the time period 14-25 years. These covariate factors were chosen on the basis of being a) previously found to be relevant predictors in fixed-effects models of cannabis use (e.g 6); and b) theoretically relevant to both the frequency of cannabis use and other illicit drug involvement.

Stressful life events – Assessed by responses to items from the Feeling Bad Scale (54) and custom-written survey items, and summed to provide an index of the number of stressful life events during each year.

Cohabitation with partner – Assessed by asking participants whether they had resided with a romantic partner during at least part of the previous year(s), and classified as yes or no.

Dependent children – Assessed by asking participants whether they had any children whom they either lived with or supported, and classified as yes or no.

Unemployment – Assessed by asking participants about their experience of unemployment in each year and classified into four levels reflecting the duration of unemployment in the year; never unemployed; < 3 months, 3-5 months; 6+ months.

Paid employment – Assessed by asking participants whether they had been in paid employment (including part-time) at any time during the previous year, and classified as yes or no.

Student status - Assessed by asking participants whether they had been a student (including part-time) at any time during the previous year, and classified as yes or no.

Frequency of prior cigarette smoking – Assessed at each year using a six-point scale ranging from non-smoker to 20+ cigarettes per day.

Frequency of previous alcohol use - Assessed via self-reported number of occasions of alcohol use over the previous year.

Alcohol abuse/dependence – Assessed at 15 and 16 years using items from the Rutgers Alcohol Problem Index (55) and at 18, 21, and 25 years with items from the CIDI (40). These data were then matched against DSM criteria (38, 39) to derive a dichotomous measure of alcohol abuse/dependence for each year.

Previous cannabis use – Using the outcome measure described above, previous cannabis use was entered into the models as a time-dynamic covariate.

Conduct/anti-social personality disorder problems – Assessed at 15 and 16 years using items from the Self-Report Early Delinquency Scale (56) and at ages 18, 21, and 25 from the Self-Report Delinquency Inventory (57) supplemented by custom-written items to assess anti-social personality disorder. These data were then matched against DSM criteria (38, 39) to derive dichotomous measures reflecting the history of conduct and anti-social personality disorder for each year.

Peer substance use and offending – Assessed on the basis of participant reports of the extent to which their friends a) used tobacco, alcohol, or illicit drugs or had problems resulting from alcohol or illicit drugs, and b) engaged in criminal offending, had problems with aggressive behavior or were in trouble with the law, α (substance) = .69-.77; α (offending) = .65-.77.

Partner substance use and offending - Assessed on the basis of participant reports of the extent to which their partner a) used tobacco, alcohol, or illicit drugs or had problems resulting from alcohol or illicit drugs, and b) engaged in criminal offending, had problems with aggressive behavior or were in trouble with the law; α (substance) = .55-.59; α (offending) = .67-.73.

Anxiety and depression – Assessed via items from the DISC (52) and from the CIDI (40). These data were then matched against DSM criteria (38, 39) to derive dichotomous measures of anxiety disorder and major depression for each year.

Statistical Methods

1. In the first stage of the analysis, the associations between the extent of cannabis at each year and rates of other illicit drug use were tabulated and tested for statistical significance using the Mantel-Haenszel chi squared test for linearity (Table 1).
2. The results in Table 1 were then modelled using a random effects generalized estimating equation model in which the log odds of other illicit drug use in a given year were modelled as a linear function of cannabis use in the year, previous illicit drug use and age. In addition the model included an age x cannabis use interaction to take account of the changing effects of cannabis at different ages. The model fitted was:

$$\text{Logit}(Y_{it}) = B_0i + B_1X_{1it} + B_2X_{2it} + B_3A_t + B_4(A_t \times X_{1it}) \quad (1)$$

where Y_{it} was other illicit drug use, X_{1it} was the level of cannabis use at age t , X_{2it} was a dichotomous measure reflecting the prior history of using other illicit drugs, and A_t was a

measure of the respondent's age centered around age 19-20. This model estimates the main effect (B1) and interaction (B4) of cannabis use net of the previous use of other illicit drugs and age. The model includes an individual-specific intercept (B0i) which is assumed to be uncorrelated with other factors in the model.

3. Two covariate adjustment approaches were used. In the first approach the random-effects model in EQ 1 was extended to include observed fixed and time dynamic covariate factors. The fitted model was:

$$\text{Logit}(Y_{it}) = B_{0i} + B_1X_{1it} + B_2X_{2it} + B_3A_t + B_4(A_t \times X_{1it}) + \sum B_j Z_{ij} + \sum B_k Z_{ikt} \quad (2)$$

where Z_{ij} represented the fixed observed covariate factors and Z_{ikt} represented observed time dynamic covariates. This model estimates the main effects and interactions of cannabis use net of previous history of other illicit drug use, age, observed fixed Z_{ij} and time dynamic Z_{ikt} covariate factors.

The second model fitted was a fixed-effects regression model:

$$\text{Logit}(Y_{it}) = B_{0i} + B_1X_{1it} + B_2X_{2it} + B_3A_t + B_4(A_t \times X_{1it}) + \sum B_k Z_{ikt} \quad (3)$$

Unlike the random-effects model in (2) this model permitted the intercept parameters B_{0i} to be correlated with the exposure variable X_{1it} . This model estimates the main effects and interactions of cannabis use net of previous illicit drug use, age, non-observed fixed covariates (including common genes and common environment) and observed time dynamic covariates. From these models estimates of the covariate adjusted odds ratios describing the relationship between cannabis use and other illicit drug use were obtained (Table 4).

4. The analyses of use of other illicit drug were then extended to analysis of: a) DSM IV defined other illicit drug abuse/dependence; and b) the diversity of drug use reported by the respondent. The analyses of the abuse/dependence criterion used random- and fixed-effects logistic models whereas the analyses of the diversity measure used random- and fixed-effects Poisson regression (Table 5). All models were fitted in Stata 8 (58).

Sample size and sample bias

The present analyses were based on samples having complete data for frequency of cannabis use and other illicit drug use during each year. These samples ranged in size from 953 to 1,025 and represented between 75% to 81% of the initial cohort of 1,265 children. 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. Missing data were omitted using listwise deletion of cases.

To examine the effects of sample losses on the representativeness of the sample, the obtained samples with complete data at each age, were compared with the remaining sample members on a series of socio-demographic measures collected at birth. This analysis suggested that there were statistically significant ($p < .01$) tendencies for the obtained samples to under-represent individuals from socially disadvantaged backgrounds characterized by low parental education, low socio-economic status and single parenthood. To address this issue, the data weighting methods described by Carlin, Wolfe, Coffey and Patton (59) were used to examine the possible implications of selection effects arising from the pattern of missing data. These analyses produced essentially the same pattern of results to those reported here, suggesting that the conclusions of this study were unlikely to have been influenced by selection bias.

Results

a) Usage of other illicit drugs

By twenty-five, 42% of the cohort had reported using illicit drugs other than cannabis. Of those reporting the use of other illicit drugs, 82% reported having used hallucinogens (ecstasy, LSD); 62% reported having used stimulants (including methamphetamine), barbiturates, or other (illicitly obtained) prescription medicines; 39% reported having used substances such as mushrooms and datura; 11% reported having used solvents; 20% reported having used cocaine; and 9% reported having used opiates including heroin and morphine.

b) Associations between frequency of cannabis use and other illicit drug use

A majority of participants reporting the use of cannabis also reported having used cannabis prior to the first use of other illicit drugs. In 98% of cases, cannabis had been used either in the same year or prior to the first use of other illicit drugs. In 86% of cases the individual reported the use of cannabis at least one year prior to the year in which other illicit drugs were first reported to have been used.

Table 1 shows the association between levels of cannabis use at each year from age 14-15 to age 24-25 and rates of usage of other illicit drugs. Each comparison is tested for significance using the Mantel-Haenszel chi squared test for linear trend. The Table shows that at all ages there were significant ($p < .0001$) linear trends for the increasing use of cannabis to be associated with the increasing use of other illicit drugs. Further inspection of the Table suggests that the strength of this association tended to decline with increasing age.

INSERT TABLE 1 HERE

To model the transition to other illicit drug use a random effects model was fitted to the data in Table 1 (see Methods). This modelled the log odds of other illicit drug use at each age as a linear function of current cannabis use, age, and previous other illicit drug use. Previous other illicit drug use was included in the model to take account of usage of other illicit drugs in previous years. To take into account of age related changes in the strength of association between cannabis and other illicit drug use, the model also included a linear cannabis by age interaction term. The results of this analysis are summarized in Table 2 which shows the fitted model coefficients, standard errors and tests of significance. The Table shows:

1. There was a significant main effect ($B = 1.63$, $SE = .11$, $p < .0001$) for previous other illicit drug use implying that the use of other illicit drugs in a given year was explained, in part, by previous other illicit drug use.
2. There was a linear main effect of level of cannabis use ($B = 1.45$, $SE = .05$, $p < .0001$) implying that independently of previous other illicit drug use, the increasing use of cannabis in a given year was associated with increasing rates of other illicit drug use in that year.
3. There was a significant age x cannabis interaction ($B = -.12$, $SE = .01$, $p < .0001$) implying that the associations between cannabis and other illicit drug use varied with age. The sign of the coefficient implies that with increasing age the slope of the dose/response relationship between cannabis and other illicit drug use declined.

INSERT TABLE 2 HERE

c) Control for confounding factors

As explained in Methods, two models were used to control for confounding factors. The first model was a random-effects model that included both observed fixed and time-dynamic factors. The second model was a fixed-effects model that adjusted for non-observed fixed effects and observed

time-dynamic covariate factors. The results of the analyses are summarized in Table 3 which shows for each model: estimates of the main effect of cannabis use and cannabis use by age interaction. The Table also summarizes the list of observed fixed and time dynamic covariate factors included in the analyses. The Table shows that:

1. The random-effects model revealed a significant main effect for frequency of cannabis use ($B = 1.12$, $SE = .07$, $p < .0001$) following control for previous other illicit drug use, fixed observed sources of confounding, and time-dynamic covariates. In addition, there was a significant age x cannabis interaction ($B = -.10$, $SE = .02$, $p < .0001$), implying that the strength of the association between frequency of cannabis use and other illicit drug use tended to decrease over time.
2. The fixed-effects model also showed that the association between frequency of cannabis use and other illicit drug use remained statistically significant after control for: previous other illicit drug use, non-observed fixed factors, and time-dynamic covariate factors. However, the coefficient for the main effect of frequency of cannabis use in the fixed-effects model ($B = .93$, $SE = .07$, $p < .0001$) was smaller than that for the random effects model.

INSERT TABLE 3 HERE

d) Effect size

To display the effect sizes implied by the fixed-effects model, the model parameters were used to estimate covariate-adjusted odds ratios for each age. The results are displayed in Table 4, which shows both estimates of odds ratios of other illicit drug use for varying levels of cannabis use, relative to non-users, at ages 14-15, 17-18, 20-21, and 24-25. The Table shows:

1. At all ages increasing use of cannabis was associated with increased odds of other illicit drug use and an increasing percentage of users.
2. The strength of association between cannabis use and other illicit drug use varied with age. At age 15 there was a very strong association, with weekly users of cannabis having estimated odds

of other illicit drug use that we over 60 times those of non-users. By age 25 this OR for weekly users had declined to 3.9.

INSERT TABLE 4 HERE

e) *Cannabis use and other illicit drug abuse/dependence and drug diversity*

The modelling process used in Tables 1-4 was applied to two further outcome measures; a) rates of DSM-IV abuse of/dependence on other illicit drugs; b) a diversity score reflecting the number of different types of other illicit drugs used. For the abuse/dependence measure random- and fixed-effects logistic regression models were fitted (see Methods). For the diversity score, random- and fixed-effects Poisson models were fitted. Table 5 shows estimates of the model coefficients. The Table shows:

1. For both outcomes the associations between frequency of cannabis use and other illicit drug involvement remained significant after adjustment for fixed and time dynamic covariate factors using the random-effects and fixed-effects model. As in previous analyses the estimates for the fixed-effects model were lower than those for the random-effects model, suggesting that the fixed-effects model was controlling for non-observed sources of confounding.
2. For both outcomes the fitted model shows significant linear age x cannabis use interactions. These interactions reflect a tendency for the association between cannabis use and other illicit drug involvement to decline over time.

INSERT TABLE 5 HERE

Discussion

In this series of analyses we have used data gathered over the course of a 25-year longitudinal study to appraise the cannabis gateway hypothesis - that the use of cannabis leads to an increased risk of using other illicit drugs. The study has several design features that address possible threats to validity that have been present in previous research into this topic: the use of a prospective design in which annual data on rates of cannabis and other illicit drug have been gathered over the period from adolescence to adulthood; the availability of extensive data on both fixed and time dynamic factors; and the use of statistical methods to control non-observed fixed factors including the effects of common genes and common environment on cannabis and other illicit drug use.

The findings of the analysis lead to two major conclusions:

1. Even after extensive control for both observed and non-observed confounders, the increasing use of cannabis was associated with the increasing use, abuse/dependence and diversity of use of other forms of illicit drugs.
2. The strength of the covariate-adjusted associations between cannabis use and other illicit drug use, abuse/dependence and diversity declined markedly with increasing age.

These findings are consistent with the conclusion that there is a cause and effect association between the use of cannabis and the use or misuse of other illicit drugs. The following lines of evidence support a causal explanation:

1. *Temporal sequencing*: The evidence from this study suggests that in the great majority of cases the use of cannabis preceded the use of other illicit drugs: in 86% of cases where other illicit drugs had been used, cannabis was used at least one year prior to the use of the illicit drugs and in 98% of cases where other illicit drugs had been used cannabis had been used either prior to or in the year other illicit drugs had been used. These figures set upper and lower limit bounds on the proportion of cases in which cannabis had been used prior to other illicit drugs: in at least 86% of cases and in at most 98% of cases the use of cannabis preceded the use of another illicit

drug. This strong temporal sequencing is consistent with the causal hypothesis and with the findings of previous studies (e.g. 17-19, 20).

2. *Dose/Response:* As shown in Table 1 there were clear tendencies for risks of other illicit drug use to increase with increasing use of cannabis. The presence of consistent dose/response relationships is again consistent with a causal hypothesis to the extent it would be expected that if the association were causal the risks of other illicit drug use would increase with increasing cannabis use.
3. *Size of Association:* The covariate-adjusted associations between weekly cannabis use and other illicit drug use range from being overwhelming strong (ORs over 60) to being strong (ORs over 3). These strong and pervasive associations are again consistent with a causal hypothesis.
4. *Resilience to Statistical Control:* The associations between cannabis use and other illicit drug use also proved to be resilient to extensive statistical control using two analysis approaches. In the first, a random-effects model was employed to control observed fixed and time dynamic confounding factors. In the second the fixed-effects regression model was used to control non-observed fixed sources of confounding (including common genes and common environment) and observed time dynamic confounding factors. Both sets of analyses showed substantial relationships between the extent of cannabis use and the risks of other illicit drug use. The size of the adjusted associations and the extent of control of confounders both argue against the view that the association can be explained by residual confounding. There appears to be a non-spurious association in which increasing use of cannabis is associated with increased risks of the usage of other illicit drugs.

Evaluation of the current findings in the context of the existing literature on the cannabis gateway

These findings of a strong relationship between the extent of cannabis use and other illicit drug use after control for confounding are consistent with results from other studies reporting similar results (e.g. 16, 23, 30, 31, 32, 60). For example, the results reported by Yamaguchi and Kandel (60, Table

2, p.676) imply that after control for covariate factors, those using cannabis had hazards of other illicit drug use that were over 20 times higher than non-users of cannabis.

A limitation of most of these studies has been failure to control non-observed sources of confounding. However, at least two studies have reported associations between cannabis use and other illicit drug use after control for non-observed sources of confounding. First, Lynskey et al (23) used a discordant twin design that controlled the associations between cannabis and other illicit drug use for non-observed common genes and common environment. The results of this study suggest that even following control for common genes and common environment those using cannabis were between 2.1 to 5.2 times more likely to use other illicit drugs. van Ours (16) used an econometric regression method (bivariate duration modelling) to adjust the association between cannabis use and cocaine use for non observed sources of confounding . This analysis found that although control for non-observed confounding factors explained much of this association, cannabis users remained at significantly increased risk of using other illicit drugs. van Ours concluded that the weak association between cannabis use and cocaine use in that sample may have been due to efforts in the Netherlands to separate the markets for soft drugs from the markets for hard drugs.

The present study adds to this evidence by showing that even after extensive control for both non observed fixed factors and observed time dynamic factors that the increasing use of cannabis was related to increased rates of other illicit drug use, abuse/dependence and diversity of use.

What is responsible for the cannabis gateway effect?

While drawing causal conclusions in the basis of correlational designs is always subject to potential uncertainty and debate (11), we believe that the evidence from the present study provides relatively compelling evidence to suggest that the use of cannabis plays a causal role in the development of other forms of illicit drug use. The evidence in favour of causality includes dose/response, temporal sequencing, size of effect, and resilience of the association to control for observed and non-observed sources of confounding. This conclusion raises important issues about the possible

mechanisms by which the use of cannabis may lead to an increased susceptibility to the misuse of other illicit drugs. There are at least three pathways by which cannabis use may lead to other illicit drug use:

1. *Biochemical Factors.* First it may be proposed that the increasing use of cannabis may lead to changes in brain chemistry that increases individual responsiveness to other illicit drugs. This view has been outlined by Schenk (61) who proposed the sensitivity hypothesis. Under the sensitivity hypothesis cannabis acts as a gateway drug by modifying individual responsiveness to drugs at a biological level. Schenk reviewed a number of studies of neurobiological activity in animals that have found that exposure to 'gateway drugs' (including cannabis) rendered animals more sensitive to the effects of other drugs, such as cocaine (i.e. more likely to self-administer another drug later). While such biochemical mediation remains a possibility, the biochemical model fails to explain a number of findings of the cannabis gateway effect in humans. While studies have found evidence suggesting an increased sensitivity to drugs following the administration of other drugs, thus perhaps explaining the persistence of *drug use*, this finding does little to explain why individuals seem to choose to use other drugs following, but not prior to, the use of cannabis, and fails to address the age-related changes in the cannabis gateway effect, such as those observed in the current study.
2. *Individual Learning:* A second explanation is that the linkages between cannabis use and other illicit drug use results from an individual learning process in which individuals first experiment with cannabis and learn that the drug has pleasurable effects and low rates of adverse side effects. These experiences then form the foundations for further experimentation with other illicit drugs. Under this model, cannabis acts as a gateway drug by providing the individual with learning experiences and reinforcement that encourages generalization of illicit drug use beyond the use of cannabis. There is little direct evidence to support this explanation. Nonetheless evidence from the Christchurch Health and Development study suggests that most users of

cannabis find their early experience with this drug to be pleasurable and to have few adverse effects (e.g. 32, 62).

3. *Differential Association*: A limitation of both the biochemical and individual learning theories is that these theories fail to take into account that the use of cannabis and other illicit drugs takes place in a social context which influences the availability of substances and attitudes to substance use. It may be suggested that the principal process by which cannabis use leads to other illicit drug use arises from the differential association of cannabis users and non users with drug culture and drug dealers. In particular, regular cannabis users will often need to remain in contact with drug dealers in order to obtain supplies of cannabis. In turn this linkage of cannabis with the illicit drug market will provide multiple opportunities for regular users to both learn about other illicit drugs and to obtain a supply of these drugs. Under this explanation cannabis acts as a gateway drug by providing an entrée into drug culture and the illicit drug market.

Alternatively, associations between cannabis use and other illicit drug use may be symptomatic of the individual's involvement in youth and drug culture. Under this explanation, increasing involvement in youth and drug culture is a time-dynamic common cause that explains the linkages between cannabis use and other illicit drug use.

Finally, it is possible that there is a reciprocal relationship in which: a) the use of cannabis encourages participation in drug and youth culture; and b) participation in drug and youth culture encourages the use of both cannabis and other illicit drugs.

At the present time which (if any) of the above theories explains the apparent gateway role of cannabis is unclear. However it is important to note that different explanations have different implications for debates on the legal status of cannabis (11, 63). The biochemical and individual learning accounts tend to imply that it is the experience of using cannabis that leads to the gateway effects. Such an account would support the positions of those who argue against the liberalization of cannabis laws. However, the differential association account implies that the gateway effects of

cannabis arise from the social context in which cannabis is used and supplied. This account would support arguments for the liberalization of cannabis laws in order to break the links between drug dealers, drug culture and the use of cannabis. The important implication of these considerations is that whilst the evidence from this study clearly favors the view that the use of cannabis encourages the use of other illicit drugs, the implications of this conclusion for cannabis policy are by no means straightforward or self evident: such evidence can be used to argue both for or against the liberalization of cannabis law depending on the underlying mechanisms that are assumed to link the use of cannabis to the use of other illicit drugs.

Developmental trends

A striking result to emerge from this analysis was the way in which the association between the use of cannabis and other illicit drug use varied with age. During adolescence the association was very strong but decline markedly with increasing age. These results suggest a developmental process in which the extent to which cannabis use increases individual susceptibility to other illicit drug use reduces with increasing age. This trend for the adverse effects of cannabis use to decline with increasing age has also been observed for other outcomes examined by this research including effects on: education (64), crime (6, 32, 65, 66), and suicidality (6, 66). There are several explanations of this trend for the adverse consequences of cannabis to decline with increasing age. These include:

1. *Social Maturity*: It may be suggested that the trend for the adverse effects of cannabis use to decline with increasing age largely reflects the consequences of increasing social maturity. In the case of other illicit drug use, it is relatively easy to see the reasons for 15 year old cannabis users being more susceptible to offers of other illicit drugs than (for example) 25-year old users. The trend could thus simply reflect the effects of increasing social maturity on the individual's ability to resist the use of other illicit drugs (see 67) for a prevention approach to gateway drug use that employed a social maturity model).

2. *Biological Maturity*: An alternative explanation is that the trend reflects differences in biological maturity with teenagers whose brains have not fully matured being more susceptible to the biochemical effects of cannabis.
3. *Recruitment effects*: A further explanation may be that the trends for the effects of cannabis to decline with age do not reflect a causal developmental process. Rather it could be suggested that it arises because those who are most susceptible to other illicit drug use tend to also take up cannabis use early. This would mean that, because of differences in the composition of the groups taking up cannabis at different ages, those who took up cannabis later would be, on average, less predisposed to other illicit drug use than those who took up cannabis early.

At the present time which (if any) of these theories explains the reasons for the size of the association between cannabis and other illicit drugs to decline with increasing age is unclear.

Limitations

There are a number of caveats that need to be imposed upon the analyses and conclusions of the current study. First, it is clear that the use of cannabis and other illicit drugs are complex outcomes that are likely to unfold over time in complex ways. In the current study we have attempted to model these complex outcomes through a series of equations that model involvement with other illicit drugs as a function of cannabis use, and adjusting for observed and non-observed sources of confounding. This raises the important question of the adequacy of the statistical models and methods in capturing the complexity of the processes involved with involvement with other illicit drugs. It is likely that, given this complexity, the statistical models we have employed give only an approximation to the true (but non-observed) state of affairs.

Second, the variables included in the analyses are based on report data that have been provided by the participants. As such these variables may be subject to various errors of measurement that may compromise the estimation of model parameters.

Third, although we have attempted to control sources of confounding, it is possible that the analyses may have omitted some important time-dynamic confounding factors. If this were the case the results may lead to an overestimation of the causal linkages between the frequency of cannabis use and later involvement in other illicit drug use.

Fourth, although the fixed-effects models used in this investigation control extensively for non-observed confounding, they may not explain all confounding, particularly for fixed confounding factors whose effects on cannabis use and other illicit drug use vary with age. Again, this may result in an overestimation of the causal linkages between the frequency of cannabis use and later illicit drug use.

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Table 1. Associations between frequency of cannabis use and risk of using other illicit drugs during each year (14-25 years).

Percentage of those using other illicit drugs each year	Frequency of Cannabis Use				p ¹
	Never	Less Than Monthly	At Least Monthly	At Least Weekly	
14- 15	0.2	6.2	50.0	71.4	<.0001
(N)	(881)	(65)	(12)	(7)	
15-16	0.1	5.0	22.2	55.6	<.0001
(N)	(769)	(139)	(27)	(18)	
16-17	0.0	2.8	17.5	41.9	<.0001
(N)	(630)	(252)	(57)	(86)	
17-18	0.1	2.5	22.0	61.2	<.0001
(N)	(598)	(242)	(82)	(103)	
18-19	0.2	2.4	19.7	45.8	<.0001
(N)	(516)	(251)	(76)	(168)	
19-20	0.3	9.1	28.1	57.8	<.0001
(N)	(506)	(243)	(96)	(166)	
20-21	1.9	12.1	39.0	61.4	<.0001
(N)	(538)	(215)	(100)	(158)	
21-22	2.1	14.4	26.0	55.0	<.0001
(N)	(473)	(264)	(77)	(189)	
22-23	3.6	20.7	36.5	62.4	<.0001
(N)	(500)	(237)	(85)	(181)	
23-24	3.8	28.9	59.5	63.5	<.0001
(N)	(524)	(249)	(74)	(156)	
24-25	5.7	31.5	53.9	61.8	<.0001
(N)	(559)	(232)	(76)	(136)	

¹ Mantel-Haenszel chi-squared test of significance.

Table 2. Parameter estimates for unadjusted random-effects association between frequency of cannabis use and later risk of using other illicit drugs.

Effect	B	SE	p
Frequency of cannabis use	1.45	(.06)	<.0001
Previous other illicit drug substance use	1.63	(.11)	<.0001
Age	.50	(.06)	<.0001
Cannabis x age	-.12	(.01)	<.0001

Table 3. Parameter estimates for random-effects and fixed-effects association between frequency of cannabis use and later risk of using other illicit drugs.

Effect	Random Effects ^{1,2}			Fixed Effects ²		
	B	SE	p	B	SE	p
Frequency of cannabis use	1.12	(.07)	<.0001	.93	(.07)	<.0001
Cannabis x age	-.10	(.02)	<.0001	-.10	(.02)	<.0001

¹ Model included the following observed fixed covariates: maternal age; maternal education; socioeconomic status at birth; average standard of living ages 0-10; family changes by age 15; parental history of offending; parental history of alcohol abuse/dependence; parental use of illicit drugs; parental attachment age 14; childhood sexual abuse; childhood physical abuse; gender; novelty seeking; neuroticism age 14; self-esteem age 15; conduct problems age 14; IQ; GPA ages 11-13; conduct problems ages 7-9; attention problems age 7-9; frequency of cigarette smoking age 14; frequency of alcohol use age 14; leaving school without qualifications.

² Model included the following observed time-dynamic factors: prior history of other illicit drug use; stressful life events; cohabitation with partner; dependent children; unemployment; paid employment; student; frequency of previous cigarette smoking; frequency of previous alcohol use; alcohol abuse/dependence; previous cannabis use; conduct problems; peer substance use; peer offending; partner substance use; partner offending; anxiety; depression.

Table 4. Estimated odds ratios (95% confidence intervals) for varying levels of cannabis use on risk of other illicit drug use from fixed-effects model.

Age	Frequency of Cannabis Use			
	Never	Less Than Monthly	At Least Monthly	At Least Weekly
14-15	1	4.1 (3.1-5.3)	16.4 (9.5-28.5)	66.7 (29.4-151.4)
17-18	1	3.1 (2.5-3.7)	9.3 (6.4-13.5)	28.5 (16.3-49.4)
20-21	1	2.3 (2.0-2.6)	5.3 (4.0-7.0)	12.2 (8.0-18.4)
24-25	1	1.6 (1.3-1.9)	2.5 (1.7-3.6)	3.9 (2.2-7.0)

Table 5. Parameter estimates for random- and fixed-effects associations between frequency of cannabis use and other illicit drug involvement.

Effect	Outcome											
	Abuse/Dependence						Diversity Score					
	Random ^{1,2}			Fixed ²			Random ^{1,2}			Fixed ²		
	B	SE	p	B	SE	p	B	SE	p	B	SE	p
Frequency of cannabis use	1.57	(.20)	<.0001	1.16	(.17)	<.0001	.90	(.04)	<.0001	.74	(.04)	<.0001
Cannabis x age	-.22	(.05)	<.0001	-.14	(.04)	<.05	-.11	(.01)	<.0001	-.11	(.01)	<.0001

¹ Includes all observed fixed covariates as in Table 3.

² Includes all time-dynamic covariates as in Table 3.