Tobacco smoking and cannabis use in a longitudinal birth cohort: Evidence of reciprocal causal relationships☆

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A R T I C L E   I N F O

A B S T R A C T

Background: There is evidence of associations between tobacco and cannabis use that are consistent with both a classical stepping-stone scenario that posits the transition from tobacco use to cannabis use ('gateway' effect of tobacco) and with the reverse process leading from cannabis use to tobacco abuse ('reverse gateway' effect of cannabis). The evidence of direct causal relationships between the two disorders is still missing.
Methods: We analysed data from the Christchurch Health and Development Study (CHDS) longitudinal birth cohort using advanced statistical modelling to control for fixed sources of confounding and to explore causal pathways. The data were analysed using both: (a) conditional fixed effects logistic regression modelling; and (b) a systematic structural equation modelling approach previously developed to investigate psychiatric co-morbidities in the same cohort.
Results: We found significant ($p < 0.05$) associations between the extent of cannabis use and tobacco smoking and vice versa, after controlling for non-observed fixed confounding factors and for a number of time-dynamic covariate factors (major depression, alcohol use disorder, anxiety disorder, stressful life events, deviant peer affiliations). Furthermore, increasing levels of tobacco smoking were associated with increasing cannabis use ($p = 0.02$) and vice versa ($p < 0.001$) over time.
Conclusions: Our results lend support to the notion of both of 'gateway' and 'reverse gateway' effects. That is, the association between tobacco and cannabis use arises from a reciprocal feedback loop involving simultaneous causation between tobacco use disorder and cannabis use disorder.

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1. Introduction

Tobacco and cannabis are two of the most abused recreational substances worldwide, ranking second and third in prevalence of use after alcohol (Degenhardt et al., 2008). Both tobacco and cannabis are mostly taken via smoking (Agrawal et al., 2012), and the two substances are often co-administered in the form of 'joints' or 'blunts' (cannabis rolled in cigar paper; Ream et al., 2008). Furthermore, many tobacco and cannabis users are co-users; that is, they use the two substances independently of each other either in

distinct occasions or in a sequence (e.g., Mayet et al., 2011; Richter et al., 2004).

A multi-criteria analysis of drug harm (Nutt et al., 2010) indicates that tobacco and cannabis are among the four most damaging recreational substances in terms of direct and indirect economic costs to society. Furthermore, it has been proposed that tobacco and cannabis may serve as gateway drugs, leading to the use and abuse of other substances (Anthony, 2012). Gateway theory has been the subject of some controversy in the literature, having been criticized in terms of both drug sequence and causal modelling (Baumrind, 1983; Degenhardt et al., 2009, 2010). However, it is clear that a better understanding of the factors involved in initiating tobacco and cannabis use may shed considerable light on the factors responsible for their use.

Tobacco users who are also cannabis users are more likely to be daily smokers and develop dependence than non-cannabis users

(Agrawal et al., 2011; Degenhardt et al., 2010; Korhonen et al., 2008, 2010; Timberlake et al., 2007). On the other hand, tobacco smokers who experiment with cannabis are more likely to progress to full-blown cannabis abuse than non-smokers (Ream et al., 2008; Timberlake et al., 2007). Using data collected from the National Household Survey on Drug Use and Health (NSDUH) in 2009, Agrawal et al. (2012) estimated that the probability to develop a cannabis use disorder was more than eight times greater in tobacco users than in non-users and that the probability to develop nicotine dependence in cannabis users was more than three-fold that of non-users. These findings are consistent both with the classical stepping-stone scenario that posits the transition from tobacco use to cannabis use and with the reverse process leading from cannabis use to tobacco abuse (reverse gateway effect of cannabis; Patton et al., 2005; Timberlake et al., 2007; Viveros et al., 2006). Indeed, there are at least three possible explanations for the comorbidity of tobacco and cannabis use disorders. First, it is possible to hypothesize the existence of common or correlated genetic and/or environmental factors that predispose the individual to both substance use disorders. A second possibility is that the association is caused by tobacco acting as a gateway drug to cannabis or vice versa. Finally, it is possible that the associations arise from a reciprocal feedback loop involving simultaneous causation between tobacco use disorder and cannabis use disorder.

Previous studies aimed at investigating these different possibilities have not been conclusive. Mayet et al. (2011), for example, used a homogenous Markov multi-state model to analyze data from a repeated cross-sectional survey to estimate the prevalence of tobacco and cannabis use disorders and their relationship. Their findings were compatible with a process mixing the gateway theory, the reverse gateway theory, and the route of administration model (Agrawal and Lynskey, 2009; Prince van Leeuwen et al., 2011). Thus, the authors concluded that longitudinal studies were necessary to explore the causal relationship between tobacco use disorder and cannabis use disorder. The need of longitudinal studies has also been stressed by Agrawal et al. (2012, 2011).

In the present study, we used data from a 35-year longitudinal study of a New Zealand birth cohort to explore the causal relationships between tobacco use and cannabis use on the basis of the prevalence and frequency of use at five time periods (ages 18, 21, 25, 30 and 35 years). The data were analysed using the same analytic approach previously developed to study the associations between major depression and both alcohol use disorder (Fergusson et al., 2009) and tobacco use (Boden et al., 2010), and between internalizing disorders and substance use disorders (Fergusson et al., 2011). This analytic method incorporates: (a) the use of conditional fixed-effects regression models, augmented by time-dynamic covariate factors, to control for non-observed sources of confounding (Hamerle and Ronning, 1995; Hausman et al., 1984; Judge et al., 1980); and (b) structural equation modelling. This combination of analytic approaches allows inferences concerning possible causal associations between cannabis use and tobacco smoking, and permits examination of the likely direction of causality in the associations between cannabis use and tobacco smoking.

2. Methods

2.1. Participants

Data were gathered during the course of the Christchurch Health and Development Study (CHDS), a study of a birth cohort of 1265 children (635 males, 630 females) born in the Christchurch (New Zealand) urban region in mid-1977. The cohort has been studied at birth, 4 months, 1 year and annually to age 16 years, and again at ages 18, 21, 25, 30, and 35 years (Fergusson and Horwood, 2001; Fergusson et al., 1989). All study information was collected on the basis of signed consent from study participants and is fully confidential, and is approved by the Canterbury (NZ) Ethics Committee.

2.2. Frequency of cannabis use (ages 17–18, 20–21, 24–25, 29–30, and 34–35 years)

At each assessment at ages 18, 21, 25, 30 and 35 years, cohort members were asked about the frequency with which they had used cannabis over the twelve-month period prior to the assessment. For the purposes of this analysis, the frequency data were classified using a three-level variable with the following class intervals: (i) no cannabis use; (ii) >0 times and <1 time per week, and (iii) $\geq$1 time per week. While these class intervals are somewhat arbitrary, it should be noted that, consistent with previous research (Fergusson and Horwood, 2000; Fergusson et al., 2002), experimentation with alternative classifications produced essentially the same conclusions to those reported here.

2.3. Tobacco smoking (ages 18, 21, 25, 30, and 35 years)

At each assessment at ages 18, 21, 25, 30 and 35 years, cohort members were asked about the frequency with which they currently smoked cigarettes. For the purposes of this analysis, the smoking frequency data were classified using a three-level variable with the following class intervals: (i) no tobacco smoking, (ii) >0 cigarettes and <10 cigarettes per day, and (iii) $\geq$10 cigarettes per day. As with the cannabis frequency data described above, the use of alternative classifications produced similar conclusions to those reported here.

2.4. Time-dynamic covariate factors (ages 18, 21, 25, 30 and 35 years)

In order to control for the effects of possible comorbid mental health and substance use disorders and the effects of stressful life events in the analyses, five time-dynamic covariate factors were obtained from the study database. These included: (a) concurrent DSM-IV major depression; (b) concurrent DSM-IV alcohol use disorder; (c) concurrent DSM-IV anxiety disorder; (d) a count measure of the number of stressful life events experienced during the twelve months prior to each assessment; and (e) a measure of the number of cohort members' deviant peers who either used illicit drugs, or were in trouble in the law. Further details of these measures are given in the Online Supplement.

2.5. Statistical analyses

Associations between frequency of cannabis use and frequency of tobacco smoking: In the first stage of the analyses, the pooled associations between the measures of the frequency of cannabis use and tobacco smoking at ages 18, 21, 25, 30, and 35 years were estimated using Generalized Estimating Equation (GEE) methods (Liang and Zeger, 1986; Zeger and Liang, 1986). Two models were fitted: one in which cannabis use predicted tobacco smoking; and a second model in which tobacco smoking predicted cannabis use. In order to address issues of non-linear trend in each of the predictors, effect proportional scoring methods were used. Specifications of these models are given in Supplementary material[1].
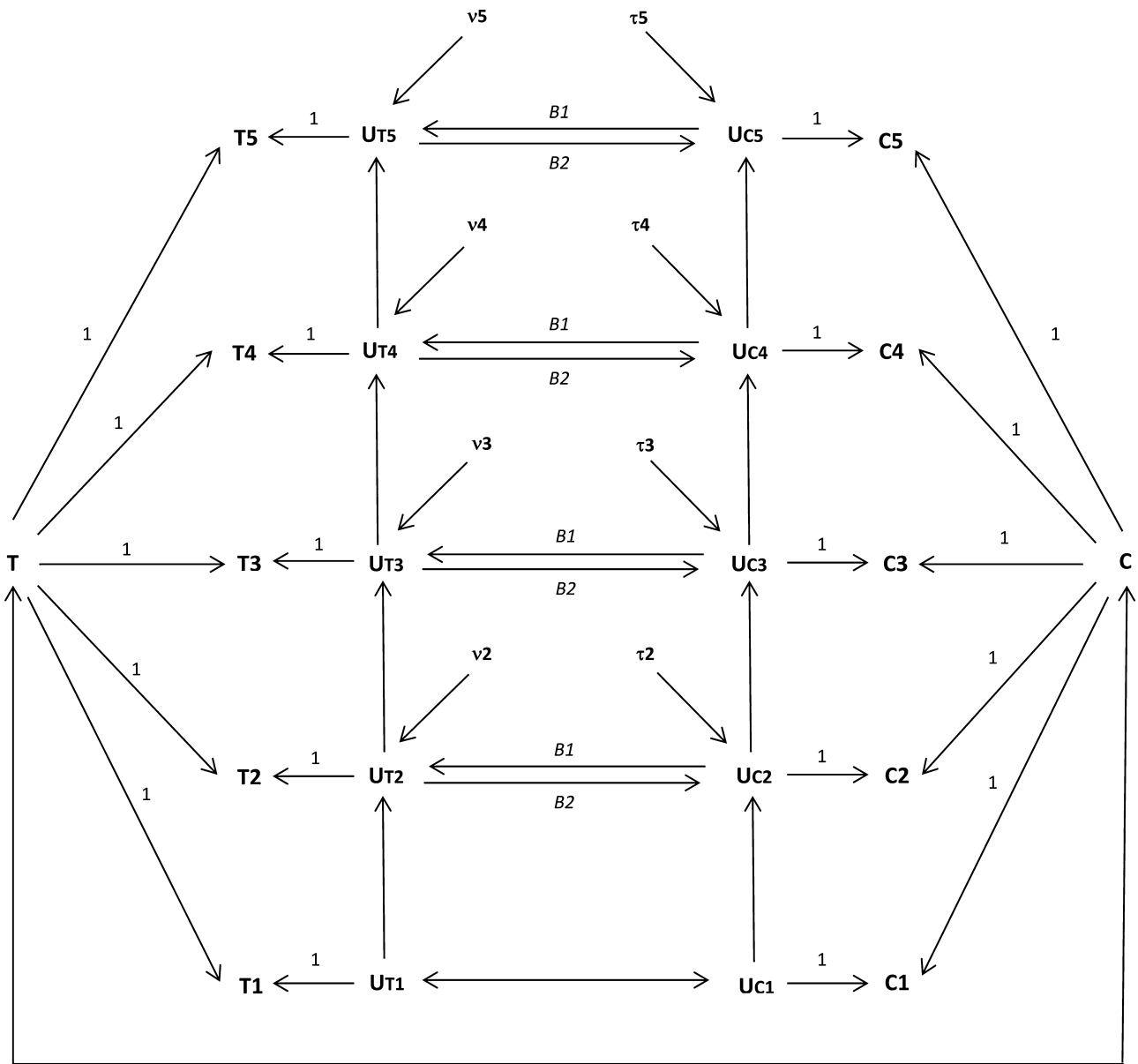
Fixed effects model for covariate adjustment: To adjust the associations between cannabis use and tobacco smoking for both: (a) non-observed fixed sources of confounding; and (b) observed time-dynamic covariate factors, conditional fixed effects logistic regression models were fitted to the joint data for each prediction model (cannabis use predicting tobacco smoking; tobacco smoking predicting cannabis use) over the measurement periods (Hamerle and Ronning, 1995; Hausman et al., 1984; Judge et al., 1980). See the Supplementary material[2] for a detailed description of the basis for the fixed effects modelling and model specification.

Structural equation modelling of reciprocal causal pathways: To examine the possibility of a reciprocal causal relationship in which cannabis use led to increased risks of tobacco smoking, and tobacco smoking led to increased risks of cannabis use, a structural equation model was fitted to the variance-covariance matrix of the repeated measures of cannabis use and tobacco smoking at each assessment (ages 18, 21, 25, 30, and 35 years), using Mplus and weighted least squares estimation. An example of the reciprocal causal model is displayed in Fig. 1. The model assumes that the reported frequency of tobacco use at these time periods (t = 1 to 5) is influenced by fixed sources of variation (T), which are constant over time, and by time-dynamic sources of variation (U_T). Likewise, the reported frequency of cannabis use is influenced by fixed sources of variation (C) and by time-dynamic sources of variation (U_C). The model allows the fixed factors T and C to be correlated. The model also assumes that U_T and U_C are linked by autoregressive processes in which past frequencies predict future frequencies. Finally, the model assumes that U_T and U_C are reciprocally related at t = 2, 3, 4, or 5, so that current U_T influences current U_C and vice versa, with these reciprocal effects assumed to be constant over time. Further details of the model assumptions and model fitting are provided in the Supplementary material[3].

Fig. 1. Reciprocal structural model of the associations between cannabis use and tobacco smoking.

2.6. Sample size and sample bias

The present analyses were based on 1025 (age 18), 1011 (age 21), 1003 (age 25), 987 (age 30), and 962 (age 35) individuals, representing 76–80% of the original cohort. To examine the effects of sample losses on sample representativeness, 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. These results suggested that there were statistically significant ($p < 0.01$) tendencies for the obtained samples to under-represent individuals from socially-disadvantaged backgrounds. To address this issue, data weighting methods described by Carlin et al. (1999) were used to re-analyze the data, producing 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.

3. Results

3.1. Patterns of cannabis use, tobacco smoking and co-use[4]

As shown in Fig. 2 and Tables 1a and 1b, more than half of the cohort (54.5%) reported smoking tobacco and/or cannabis at

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[4] Throughout this paper, the term co-use indicates the use of both tobacco and cannabis in distinct occasions by the same individual, and not the co-administration of the two drugs via 'joints' or 'blunts'.
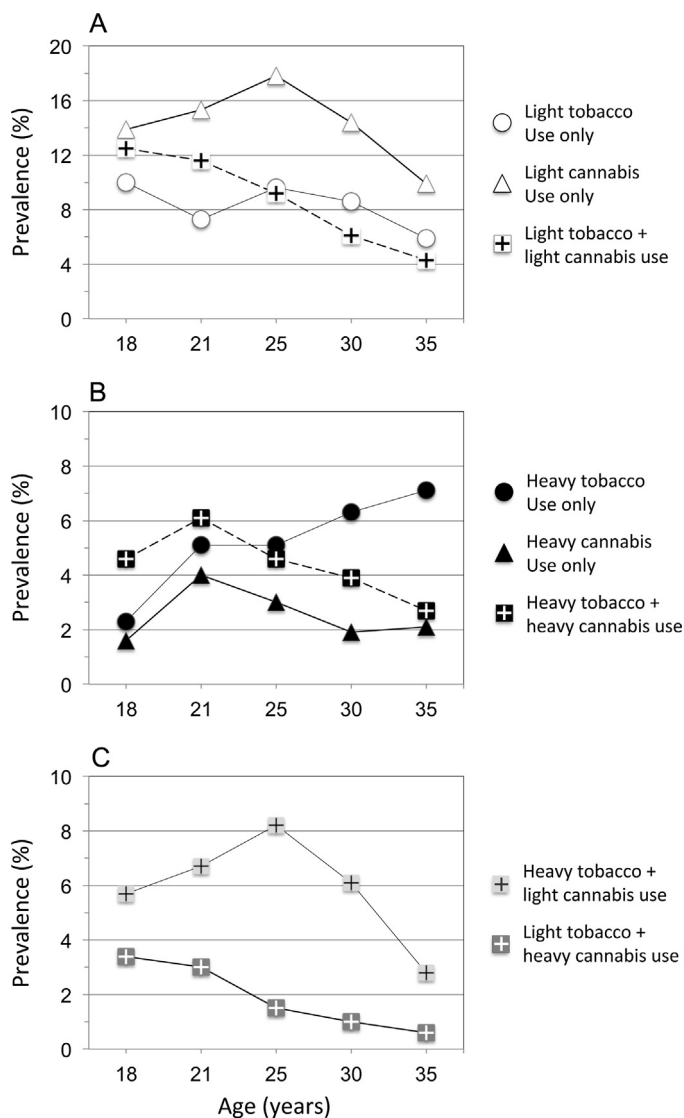
Fig. 2. Prevalence of use in the past 12 months at ages 18, 21, 25, 30, and 35 years, for: (A) 'light tobacco smokers-only' (<10 cigarettes per day), 'light cannabis users-only' (<1 time per week), and light co-users; (B) 'heavy tobacco smokers-only' (>10 cigarettes per day), 'heavy cannabis users-only' (≥1 time per week), and heavy co-users; (C) heavy tobacco-light cannabis co-users and light tobacco-heavy cannabis co-users.

age 18 years. The overall number of users peaked at age 21 and progressively decreased, so that at age 35 only 35.3% of the cohort was still smoking tobacco and/or cannabis. Fig. 2 also illustrates the changes in the prevalence of tobacco and cannabis co-use and indicates that the decline in use concerned all types of users and co-users, except those who were 'heavy tobacco smokers-only' (>10 cigarettes per day) or 'heavy cannabis users-only' (≥1 time per week). Fig. 3A shows that among 'tobacco smokers-only' the proportion of heavy users more than tripled from age 18 years to age 35 years. This was not the case for either 'cannabis users-only' or for co-users (Fig. 3B and C).

3.2. Associations between cannabis use and tobacco smoking

Table 1a shows the associations between the frequency of cannabis use and the probability of being a tobacco smoker at ages 18, 21, 25, 30, and 35 years. Table 1b shows the frequency of tobacco smoking and the probability of using cannabis at ages 18, 21, 25, 30, and 35 years. The data in both tables were analysed using a

Table 1a

Associations between frequency of cannabis use and probability of tobacco smoking, ages 18, 21, 25, 30, and 35 years.

Age	Level of cannabis use	n	% reporting tobacco smoking
18	None	598	22.1
	<Weekly	329	56.5
	≥Weekly	98	83.7
21	None	538	23.4
	<Weekly	340	54.4
	≥Weekly	133	69.2
25	None	559	26.3
	<Weekly	353	49.3
	≥Weekly	91	67.0
30	None	657	21.5
	<Weekly	262	45.0
	≥Weekly	68	72.1
35	None	747	16.7
	<Weekly	163	41.7
	≥Weekly	52	61.5
Population-averaged rates	%		OR (95% CI)
None	21.7		1 (–)
<Weekly	49.9		5.30 (4.24–6.62)
≥Weekly	67.6		28.22 (18.17–43.82)

random effects GEE model to estimate the associations between: (i) cannabis use and tobacco smoking, and (ii) tobacco smoking and cannabis use. Both analyses show the presence of strong linear associations ($p < 0.0001$) between the extent of cannabis/tobacco use and the probabilities of tobacco smoking/cannabis use, as indicated by the relative OR's.

3.3. Adjustments for confounding

Tables 2a and 2b show the results of analyses controlling for both (i) non-observed fixed confounding factors; and (ii) a number of time-dynamic covariate factors, including: major depression; alcohol use disorder; anxiety disorder; stressful life events; and

Table 1b

Associations between frequency of tobacco smoking and probability of cannabis use, ages 18, 21, 25, 30, and 35 years.

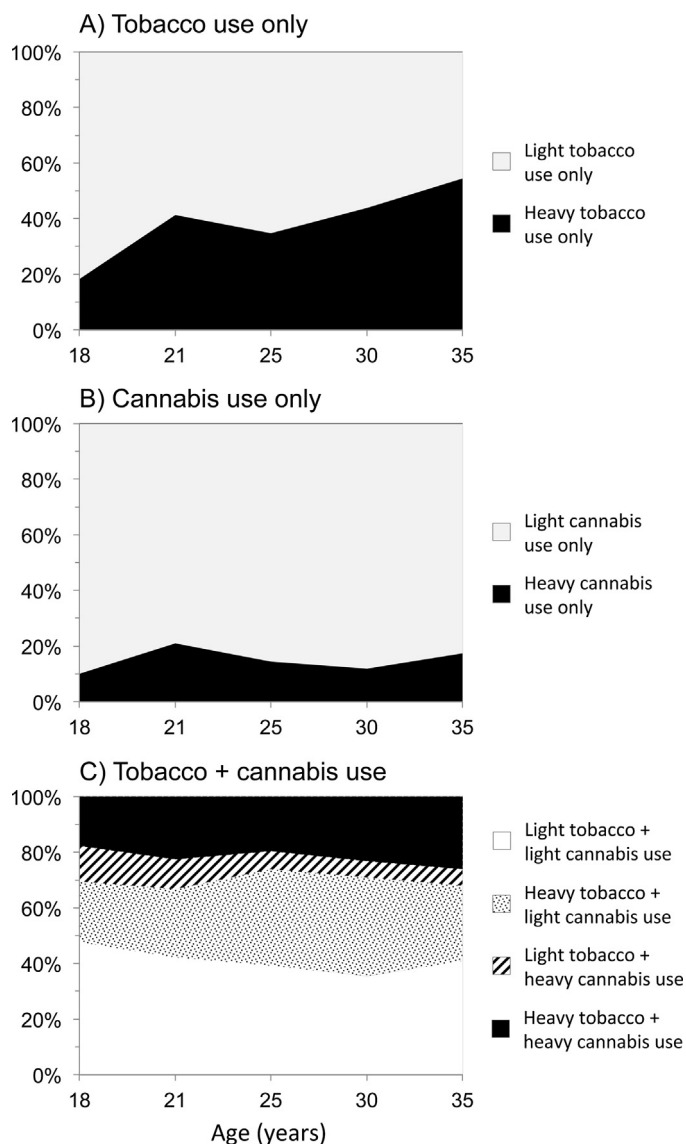| Age	Level of cigarette smoking	n	% reporting cannabis use
18	None	625	25.4
	<10/day	271	60.1
	10+/day	129	81.4
21	None	608	37.2
	<10/day	221	66.5
	10+/day	182	71.4
25	None	621	33.7
	<10/day	203	52.7
	10+/day	179	71.6
30	None	677	23.8
	<10/day	149	47.0
	10+/day	161	61.5
35	None	737	15.6
	<10/day	104	45.2
	10+/day	121	43.8
Population-averaged rates	%		OR (95% CI)
None	25.7		1 (–)
<10/day	56.3		5.51 (4.49–6.76)
10+/day	66.7		30.57 (20.09–45.60)

Fig. 3. Proportion of light versus heavy use (at ages 18, 21, 25, 30, and 35 years) for: (A) tobacco smokers-only; (B) cannabis users-only; (C) co-users. For the definition of 'light' and 'heavy' see text and Fig. 1.

deviant peer affiliations. Table 2a shows the estimates of the covariate-adjusted coefficients for the prediction of smoking from cannabis use and Table 2b those for the prediction of cannabis use from smoking. Both analyses showed that control for non-observed fixed factors and time-dynamic covariate factors reduced the magnitude of the associations between tobacco smoking and cannabis use. Nonetheless, the adjusted associations remained statistically significant ($p < 0.05$) and substantial, suggesting that the

Table 2a
Associations between frequency of cannabis use and probability of tobacco smoking, after adjustment for both: (a) non-observed fixed sources of confounding; and (b) time-dynamic covariate factors.

	Cigarette smoking
Level of cannabis use	OR (95% CI)
None	1 (–)
<Weekly	2.90 (2.34–3.58)
≥Weekly	8.41 (5.48–12.82)

Statistically significant ($p < 0.05$) time dynamic covariate factors: major depression; alcohol use disorder; anxiety disorder; life stress; deviant peer affiliation.

Table 2b
Associations between frequency of tobacco smoking and probability of cannabis use, after adjustment for both: (a) non-observed fixed sources of confounding; and (b) time-dynamic covariate factors.

	Cannabis use
Level of cigarette smoking	OR (95% CI)
None	1 (–)
<10/day	2.69 (2.21–3.28)
10+/day	7.24 (4.88–10.76)

Statistically significant ($p < 0.05$) time dynamic covariate factors: major depression; alcohol use disorder; life stress; deviant peer affiliation.

associations between cannabis use and tobacco smoking could not be accounted for by non-observed sources of confounding, or time-dynamic covariate factors.

3.4. Testing for reverse causality

The findings in Tables 1a and 1b and 2a and 2b are consistent with three general explanations of the associations between cannabis use and tobacco smoking: (1) cannabis use leads to tobacco smoking; (2) tobacco smoking leads to cannabis use; and (3) there is a reciprocal causal relationship in which both (1) and (2) hold simultaneously. One advantage of longitudinal data is that it is possible to fit structural equation models (SEMs) that permit reciprocal causal pathways (Boden et al., 2010; Fergusson et al., 2009). To examine this possibility, the SEM depicted in Fig. 1 was fitted to the data (see Section 2) using Mplus (the full set of coefficients is available upon request from the corresponding author).

The method of modelling (described in detail in the Supplementary material[5]) estimates two key parameters of interest: (i) the parameter B_1 reflecting the causal effect of cannabis use on the level of tobacco smoking, and (ii) the parameter B_2 reflecting the causal effect of tobacco smoking on the level of cannabis use.

The model depicted in Fig. 1 was fitted to the repeated measures data on levels of tobacco use and cannabis use over the five time periods from age 18–35. The model showed an excellent fit to the observed data [model $\chi^2(25) = 32.7$, $p = 0.14$; RMSEA = 0.019; CFI = 0.99]. Further, the model showed that after control for non-observed fixed sources of confounding, there was evidence of modest but statistically significant reciprocal associations in which: (i) increasing levels of cannabis use were associated with increasing tobacco smoking ($B_1 = 0.099$; SE = 0.03; 95% CI: 0.040–0.158; $p < 0.001$), and (ii) increasing levels of tobacco smoking were associated with increasing cannabis use ($B_2 = 0.066$; SE = 0.027; 95% CI: 0.013–0.119; $p = 0.02$).

4. Discussion

The present study analysed data from the Christchurch Health and Development Study (CHDS) longitudinal birth cohort using advanced statistical modelling to control for fixed sources of confounding, and to explore causal pathways in the associations between cannabis use and tobacco smoking. The findings of these analyses and their implications are outlined below.

4.1. Patterns of tobacco smoking and cannabis use

More than half of the CHDS cohort reported using tobacco and/or cannabis at age 18 years, with an overall prevalence of 54.5%. At this age, most of these users (regardless of the frequency of use) were co-users. This pattern is consistent with previous studies

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[5] Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:10.1016/j.drugalcdep.2015.02.015.

investigating a similar age bracket (e.g., Agrawal et al., 2011). The overall prevalence of use peaked at age 21 and then progressively decreased to 35.3% by age 35 years.

However, age-dependent changes in the prevalence of use were very different as a function of drug and of intensity of use. The prevalence of use at age 35 years was in fact half that observed at age 18 years for light (<weekly) and heavy (≥weekly) cannabis users (−47.5% and −43.75%, respectively), and for light tobacco smokers (<10 cigarettes per day; −59.1%). In contrast, the prevalence of heavy tobacco smoking at age 35 years was exactly the same observed at age 18 years. More specifically, there was an age-related decline for all types of users and co-users, except for those who were 'heavy tobacco smokers-only' or 'heavy cannabis users-only' (see Fig. 1), indicating the emergence of more selective drug preferences. This was particularly true of heavy tobacco smokers-only, whose prevalence increased more than 200% from age 18 years to age 35 years (see Figs. 1C and 2A) whereas for heavy cannabis users-only the increase was only by 31%, confirming that the addictive potential of tobacco is much greater than that of cannabis, whereas the probability of remission from dependence is much lower (Lopez-Quintero et al., 2011a, 2011b).

An important aspect of the CHDS birth cohort is that the prevalence of use for cannabis-only was comparable to that for tobacco-only at ages 18 and 35, a pattern that is characteristic of New Zealand and Australia (e.g., Degenhardt et al., 2008; Swift et al., 2012) and that stands in sharp contrast with that observed in most other countries, where the prevalence of tobacco use is much higher than that of cannabis (e.g., Agrawal et al., 2012; Degenhardt et al., 2008). The similarity in the prevalence of tobacco and cannabis use is ideally suited to investigate the reciprocal influences between the two conditions.

4.2. Reciprocal influences between tobacco smoking and cannabis use

In agreement with previous studies (Agrawal et al., 2011; Degenhardt et al., 2010; Korhonen et al., 2008, 2010; Ream et al., 2008; Timberlake et al., 2007), we found a significant association between tobacco smoking and cannabis use. Light cannabis users had approximately five times greater odds of being tobacco smokers than non-users. Also the odds of light tobacco smokers of being cannabis users were about five-fold those of non-smokers. The odds of co-use greatly increased in heavy users. Both heavy tobacco smokers and heavy cannabis users were about thirty times more likely to co-use the other substance than the respective non-users.

One possible explanation for these associations is that they arose because of common confounding factors, including non-observed fixed effects as well as time dynamic covariate factors, such as concurrent psychiatric disorders (major depression, alcohol use disorder, and anxiety disorder), stressful life events and deviant peer affiliations. However, significant and robust associations remained evident even after adjustment for both non-observed fixed confounding and time-dynamic covariate factors, suggesting that the associations between cannabis use and tobacco use could not be explained by confounding. After adjustment, light users of either substance had approximately three times the adjusted odds of also using the other substance relative to the respective non-users. In heavy users of either substance the adjusted odds were seven to eight times greater than those of the respective non-users. This pattern of findings suggests a possible reciprocal causal association in which cannabis use increases the risk of tobacco use, and vice-versa.

To explore the possible pathways between tobacco smoking and cannabis use, structural equation modelling was used to fit a reciprocal causation model. This analysis suggested that the best-fitting model was one in which there was a bidirectional association between tobacco smoking and cannabis smoking, in which: (i) the

use of one substance leads to the use the other substance; and (ii) the greater the intensity of use of one substance the greater the intensity of use of the other substance.

To the best of our knowledge, this is the first longitudinal study to investigate the reciprocal causal relationships between tobacco smoking and cannabis use. Our findings confirm and extend those other longitudinal studies concerned with unidirectional influences of tobacco use on cannabis use or vice versa. A 10-year cohort study conducted by Patton et al. (2005) investigated the role of cannabis use in the later initiation of tobacco use and progression to dependence. They found that at least one report of weekly cannabis use in the teens was associated to a more than eight-fold increase in the odds of later initiation of tobacco use whereas daily cannabis use at age 21 years was associated to a more than three-fold increase in the odds of progressing to tobacco dependence. A more recent longitudinal study by Prince van Leeuwen et al. (2014) examined whether tobacco use during adolescence affected the likelihood to abuse cannabis. They found that both early-onset tobacco use and continued tobacco use in adolescence doubled the likelihood of developing a cannabis use disorder.

The findings reported here have important implications for the 'gateway' hypotheses, which posits a progression in drug use, beginning with tobacco and alcohol, moving on to cannabis, and then to other illicit drugs (Botvin et al., 2000; Kandel and Faust, 1975; Kandel, 1984; Kandel et al., 1992; Lynskey et al., 2003). The nature of these "gateway" effects is a matter of some debate (Degenhardt et al., 2010; Fergusson et al., 2006; Kandel et al., 2006; MacCoun, 2006; Morral et al., 2002; Prince van Leeuwen et al., 2011; Vanyukov et al., 2012). In particular, it is not clear whether the predictive association between cannabis and other illicit drug use is causal or reflects confounding factors (Fergusson et al., 2006; Hall and Lynskey, 2005; Kandel and Faust, 1975; Kandel, 1984; Kandel et al., 2006; MacCoun, 2006; Morral et al., 2002). Furthermore, there is data suggesting a "reverse gateway" effect of cannabis use on tobacco use (Patton et al., 2005; Viveros et al., 2006). The systematic structural equation model used in the present study indicates the simultaneous occurrence of 'gateway' and 'reverse gateway' effects. That is, the association between tobacco and cannabis use arises from a reciprocal feedback loop involving simultaneous causation between tobacco use and cannabis use.

With the present study adding to the growing evidence concerning a possible gateway role of tobacco in linkages with cannabis and other illicit drugs, further questions arise concerning the mechanisms underpinning these linkages. The route of administration model (Agrawal and Lynskey, 2009) would suggest that the origins of these linkages are either physiological or cultural in nature, in which the use of either tobacco or cannabis is increased by: (a) the act of smoking one or the other substance causes aero-respiratory changes; and/or (b) social and cultural practices in which tobacco and cannabis are consumed simultaneously (via "joints" or "blunts"). Further research is necessary to better distinguish between these accounts of the linkages between tobacco and cannabis use.

A further possible explanation for the observed associations between cannabis and tobacco is the common liability model (Prince van Leeuwen et al., 2011), in which genetic and individual factors are thought to increase the risk of the use of multiple substances. However, it would seem to be the case that such factors should have been accounted for in the present analyses by: (a) the use of conditional fixed-effects models; and (b) the correlated latent indices for cannabis and tobacco in the structural models.

4.3. Limitations of the study

It is important to recognize that the conclusions drawn in this analysis rely on some underlying assumptions. The most pervasive

of these assumptions is that the pattern of causal relationships can be modelled as a stable causal process that was operative throughout the course of this study. This is clearly a strong assumption, but it is essential for both the fixed-effects and reciprocal-causes models. Additional research is required to verify whether our assumption is correct. It is also possible that our structural equations do not adequately reflect the complexity of all the factors at play, an issue that can be addressed only by further investigations based on models partly or radically different from the one used here. Finally, it should also be noted that specific instances of co-use of cannabis and tobacco (e.g. rolled together in "joints") was not measured in the present study.

Author disclosures

Contributors

The collaboration between research centres was established by AB, DMF, LJH, and GTH. AB, JMB, and SDP performed literature searches. JMB and LJH analysed the data. AB and DMF designed the study and reviewed the analyses. JMB, DMF, and LJH collected the data. All authors contributed to the writing of the draft article, and approved of the final manuscript.

Conflict of interest

No conflict declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drugalcdep.2015.02.015.

References

Agrawal, A., Budney, A.J., Lynskey, M.T., 2012. The co-occurring use and misuse of cannabis and tobacco: a review. Addiction 107, 1221–1233.

Agrawal, A., Lynskey, M.T., 2009. Tobacco and cannabis co-occurrence: does route of administration matter? Drug Alcohol Depend. 99, 240–247.

Agrawal, A., Scherrer, J.F., Lynskey, M.T., Sartor, C.E., Grant, J.D., Haber, J.R., Madden, P.A., Jacob, T., Bucholz, K.K., Xian, H., 2011. Patterns of use, sequence of onsets and correlates of tobacco and cannabis. Addict. Behav. 36, 1141–1147.

Anthony, J.C., 2012. Steppingstone and gateway ideas: a discussion of origins, research challenges, and promising lines of research for the future. Drug Alcohol Depend. 123 (Suppl. 1), S99–S104.

Baumrind, D., 1983. Specious causal attributions in the social sciences: the reformulated stepping-stone theory of heroin use as exemplar. J. Pers. Soc. Psychol. 45, 1289–1298.

Boden, J.M., Fergusson, D.M., Horwood, L.J., 2010. Cigarette smoking and depression: tests of causal linkages using a longitudinal birth cohort. Br. J. Psychiatry, 440–446.

Botvin, G.J., Griffin, K.W., Diaz, T., Scheier, L.M., Williams, C., Epstein, J.A., 2000. Preventing illicit drug use in adolescents: long-term follow-up data from a randomized control trial of a school population. Addict. Behav. 25, 769–774.

Carlin, J.B., Wolfe, R., Coffey, C., Patton, G.C., 1999. Tutorial in biostatistics, analysis of binary outcomes in longitudinal studies using weighted estimating equations and discrete-time survival methods: prevalence and incidence of smoking in an adolescent cohort. Stat. Med. 18, 2655–2679.

Degenhardt, L., Chiu, W.T., Conway, K., Dierker, L., Glantz, M., Kalaydjian, A., Merikangas, K., Sampson, N., Swendsen, J., Kessler, R.C., 2009. Does the 'gateway' matter? Associations between the order of drug use initiation and the development of drug dependence in the National Comorbidity Study Replication. Psychol. Med. 39, 157–167.

Degenhardt, L., Chiu, W.T., Sampson, N., Kessler, R.C., Anthony, J.C., Angermeyer, M., Bruffaerts, R., de Girolamo, G., Gureje, O., Huang, Y., Karam, A., Kostyuchenko, S., Lepine, J.P., Mora, M.E., Neumark, Y., Ormel, J.H., Pinto-Meza, A., Posada-Villa, J., Stein, D.J., Takeshima, T., Wells, J.E., 2008. Toward a global view of alcohol, tobacco, cannabis, and cocaine use: findings from the WHO World Mental Health Surveys. PLoS Med. 5, 1053–1067.

Degenhardt, L., Dierker, L., Chiu, W.T., Medina-Mora, M.E., Neumark, Y., Sampson, N., Alonso, J., Angermeyer, M., Anthony, J.C., Bruffaerts, R., de Girolamo, G., de Graaf, R., Gureje, O., Karam, A.N., Kostyuchenko, S., Lee, S., Lépine, J.P., Levinson, D., Nakamura, Y., Posada-Villa, J., Stein, D., Wells, J.E., Kessler, R.C., 2010. Evaluating the drug use gateway theory using cross-national data: consistency and associations of the order of initiation of drug use among participants in the WHO World Mental Health Surveys. Drug Alcohol Depend. 108, 84–97.

Fergusson, D.M., Boden, J.M., Horwood, L.J., 2006. Cannabis use and other illicit drug use: testing the cannabis gateway hypothesis. Addiction 101, 556–569.

Fergusson, D.M., Boden, J.M., Horwood, L.J., 2009. Tests of causal linkages between alcohol abuse or dependence and major depression. Arch. Gen. Psychiatry 66, 260–266.

Fergusson, D.M., Boden, J.M., Horwood, L.J., 2011. Structural models of the comorbidity of internalizing disorders and substance use disorders in a longitudinal birth cohort. Soc. Psychiatry Psychiatr. Epidemiol. 46, 933–942.

Fergusson, D.M., Horwood, L.J., 2000. Does cannabis use encourage other forms of illicit drug use? Addiction 95, 505–520.

Fergusson, D.M., Horwood, L.J., 2001. The Christchurch Health and Development Study: review of findings on child and adolescent mental health. Aust. N.Z. J. Psychiatry 35, 287–296.

Fergusson, D.M., Horwood, L.J., Shannon, F.T., Lawton, J.M., 1989. The Christchurch Child Development Study: a review of epidemiological findings. Paediatr. Perinat. Epidemiol. 3, 278–301.

Fergusson, D.M., Horwood, L.J., Swain-Campbell, N.R., 2002. Cannabis use and psychosocial adjustment in adolescence and young adulthood. Addiction 97, 1123–1135.

Hall, W., Lynskey, M., 2005. Is cannabis a gateway drug? Testing hypotheses about the relationship between cannabis use and the use of other illicit drugs. Drug Alcohol Rev. 24, 39–48.

Hamerle, A., Ronning, G., 1995. Panel analysis for qualitative variables. In: Arminger, G., Clogg, C.C., Sobel, M.E. (Eds.), Handbook of Statistical Modeling for the Social and Behavioral Sciences. Plenum Press, New York, NY, pp. 401–451.

Hausman, J., Hall, B.H., Griliches, Z., 1984. Econometric models for count data with an application to the patents—R & D relationship. Econometrica 52, 909–938.

Judge, G.E., Griffiths, W.E., Hill, R.C., Lee, T. (Eds.), 1980. The Theory and Practice of Econometrics. John Wiley & Sons, New York, NY.

Kandel, D., Faust, R., 1975. Sequences and stages in patterns of adolescent drug use. Arch. Gen. Psychiatry 32, 923–932.

Kandel, D.B., 1984. Marijuana users in young adulthood. Arch. Gen. Psychiatry 41, 200–209.

Kandel, D.B., Yamaguchi, K., Chen, K., 1992. Stages of progression in drug involvement from adolescence to adulthood: further evidence for the gateway theory. J. Stud. Alcohol 53, 447–457.

Kandel, D.B., Yamaguchi, K., Klein, L.C., 2006. Testing the gateway hypothesis. Addiction 101, 470–476.

Korhonen, T., Huizink, A.C., Dick, D.M., Pulkkinen, L., Rose, R.J., Kaprio, J., 2008. Role of individual, peer and family factors in the use of cannabis and other illicit drugs: a longitudinal analysis among Finnish adolescent twins. Drug Alcohol Depend. 97, 33–43.

Korhonen, T., Prince van Leeuwen, A., Reijneveld, S.A., Ormel, J., Verhulst, F.C., Huizink, A.C., 2010. Externalizing behavior problems and cigarette smoking as predictors of cannabis use: the TRAILS Study. J. Am. Acad. Child Adolesc. Psychiatry 49, 61–69.

Liang, K.-Y., Zeger, S.L., 1986. Longitudinal data analysis using generalized linear models. Biometrika 73, 13–22.

Lopez-Quintero, C., Hasin, D.S., de Los Cobos, J.P., Pines, A., Wang, S., Grant, B.F., Blanco, C., 2011a. Probability and predictors of remission from life-time nicotine, alcohol, cannabis or cocaine dependence: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Addict. Biol. 106, 657–669.

Lopez-Quintero, C., Pérez de los Cobos, J., Hasin, D.S., Okuda, M., Wang, S., Grant, B.F., Blanco, C., 2011b. Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: results of the National

Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Drug Alcohol Depend. 115, 120–130.

Lynskey, M.T., Heath, A.C., Bucholz, K.K., Slutske, W.S., Madden, P.A.F., Nelson, E.C., Statham, D.J., Martin, N.G., 2003. Escalation of drug use in early-onset cannabis users vs co-twin controls. JAMA 289, 427–433.

MacCoun, R., 2006. Competing accounts of the gateway effect: the field thins, but still no clear winner. Addiction 101, 470–476.

Mayet, A., Legleye, S., Chau, N., Falissard, B., 2011. Transitions between tobacco and cannabis use among adolescents: a multi-state modeling of progression from onset to daily use. Addict. Behav. 36, 1101–1105.

Morral, A.R., McCaffrey, D.F., Paddock, S.M., 2002. Reassessing the marijuana gateway effect. Addiction 97, 1493–1504.

Nutt, D.J., King, L.A., Phillips, L.D., Independent Scientific Committee on Drugs, 2010. Drug harms in the UK: a multicriteria decision analysis. Lancet 376, 1558–1565.

Patton, G.C., Coffey, C., Carlin, J.B., Sawyer, S.M., Lynskey, M., 2005. Reverse gateways? Frequent cannabis use as a predictor of tobacco initiation and nicotine dependence. Addiction 100, 1518–1525.

Prince van Leeuwen, A., Creemers, H.E., Verhulst, F.C., Vollebergh, W.A.M., Ormel, J., van Oort, F.V.A., Huizink, A.C., 2014. Legal substance use and the development of a DSM-IV cannabis use disorder during adolescence: the TRAILS study. Addiction 109, 303–311.

Prince van Leeuwen, A., Verhulst, F.C., Reijneveld, S.A., Vollebergh, W.A., Ormel, J., Huizink, A.C., 2011. Can the gateway hypothesis, the common liability model and/or, the route of administration model predict initiation of cannabis use

during adolescence? A survival analysis—the TRAILS study. J. Adolesc. Health Care 48, 73–78.

Ream, G.L., Benoit, E., Johnson, B.D., Dunlap, E., 2008. Smoking tobacco along with marijuana increases symptoms of cannabis dependence. Drug Alcohol Depend. 95, 199–208.

Richter, K.P., Kaur, H., Resnicow, K., Nazir, N., Mosier, M.C., Ahluwalia, J.S., 2004. Cigarette smoking among marijuana users in the United States. Subst. Abuse 25, 35–43.

Swift, W., Coffey, C., Degenhardt, L., Carlin, J.B., Romaniuk, H., Patton, G.C., 2012. Cannabis and progression to other substance use in young adults: findings from a 13-year prospective population-based study. J. Epidemiol. Comm. Health 66, e26.

Timberlake, D.S., Haberstick, B.C., Hopfer, C.J., Bricker, J., Sakai, J.T., Lessem, J.M., Hewitt, J.K., 2007. Progression from marijuana use to daily smoking and nicotine dependence in a national sample of U.S. adolescents. Drug Alcohol Depend. 88, 272–281.

Vanyukov, M.M., Tarter, R.E., Kirillova, G.P., Kirisci, L., Reynolds, M.D., Kreek, M.J., Conway, K.P., Maher, B.S., Iacono, W.G., Bierut, L., Neale, M.C., Clark, D.B., Ridenour, T.A., 2012. Common liability to addiction and gateway hypothesis: theoretical, empirical and evolutionary perspective. Drug Alcohol Depend. 123, S3–S17.

Viveros, M.P., Marco, E.M., File, S.E., 2006. Nicotine and cannabinoids: parallels, contrasts and interactions. Neurosci. Biobehav. Rev. 30, 1161–1181.

Zeger, S.L., Liang, K.-Y., 1986. Longitudinal data analysis for discrete and continuous outcomes. Biometrics 42, 121–130.