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A twin study of early cannabis use and subsequent use and abuse/dependence of other illicit drugs

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ABSTRACT

Introduction. Cannabis use is strongly associated with the use and abuse/dependence of other illicit drugs. Gateway and common liabilities models have been employed to explain this relationship. We sought to examine this association using a combination of the discordant twin design and modeling methods.

Method. We assess the relationship between early cannabis use and the subsequent use and abuse/dependence of other illicit drugs in a population-based sample of male and female twin pairs using four analyses: (i) analysis of the association between early cannabis use and other illicit drug use and abuse/dependence in the entire sample of twins, (ii) assessment of the influence of early cannabis use in twin 1 on twin 2's use or abuse/dependence of other illicit drugs, (iii) use of twin pairs discordant for early cannabis use in a discordant twin design and (iv) a model-fitting procedure.

Results. We found: (i) a strong association between early cannabis use and use and abuse/dependence of other illicit drugs in the sample, (ii) twin 1's early cannabis use is significantly associated with the twin 2's other illicit drug use, (iii) the role of correlated genetic factors with some evidence for a causal influence, and (iv) the correlated liabilities model fits the data well.

Conclusions. Early cannabis use is strongly associated with other illicit drug use and abuse/dependence. The relationship arises largely due to correlated genetic and environmental influences with persisting evidence for some causal influences.

INTRODUCTION

Epidemiological studies report a substantial relationship between the use of cannabis and other illicit drugs (Kandel *et al.* 1992; Golub & Johnson, 1994; Fergusson & Horwood, 2000; Morral *et al.* 2002*a*; Lynskey *et al.* 2003). Cannabis has been proposed as a gateway drug for subsequent use and abuse/dependence of other illicit drugs such that cannabis use has a significant causal influence on the subsequent use of other illicit drugs. In contrast, the correlated liabilities model proposes that cannabis use and other illicit drug use are associated because both drugs are influenced by a single common liability.

The relative validity of the gateway and common liability models has been the topic of intense debate since the early 1970s. Epidemiological studies present evidence for the common liability model (Huba *et al.* 1981; Donovan & Jessor, 1985; Hays *et al.* 1987; Ellickson *et al.* 1992; MacCoun, 1998; Morral *et al.* 2002*a*, *b*) and the gateway model (Adler & Kandel, 1981; O'Donnell & Clayton, 1982; Yamaguchi & Kandel, 1984; Blaze-Temple & Lo, 1992; Kandel *et al.* 1992; Kandel & Yamaguchi, 1993). While

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these studies show a high degree of association between cannabis and other illicit drug use, they do not definitively address the nature of the association (MacCoun, 1998). Hence, it is still unknown whether cannabis use has a direct causal influence on illicit drug use or whether the two are related by a common liability, or if the association results from a combination of correlated and causal processes.

The gateway model and the correlated liabilities models are not antithetic to each other. Information from twin pairs can be helpful in examining these models. In particular, the discordant twin design can compare the risk of subsequent other illicit drug use in twin pairs discordant for cannabis use. A recent study by Lynskey and colleagues analyzed this relationship and found that, compared to their non-user co-twins, twins with early cannabis use had a 2·6–5·2 times higher risk of using other illicit drugs (Lynskey *et al*. 2003).

Yet another unexplored option for examining the relationship between drug categories is model-fitting. This method, though limited by certain assumptions, employs all the available data in an efficient manner. This combination of methods, each with strengths and limitations, allows for a more complete examination of the nature of the relationship between early cannabis use and the subsequent use of other illicit drugs.

Goals

The present manuscript has the following goals:

(1) To test the association between early cannabis use and the subsequent use and abuse/dependence of other illicit drugs, within an individual, in a population-based sample of twins.

(2) To assess the extent to which early cannabis use in twin 1 predicts the subsequent use or abuse/dependence of other illicit drugs in twin 2 after controlling for twin 2's early cannabis use.

(3) To test the association between early cannabis use and use and abuse/dependence of other illicit drugs in a discordant twin design, examining the MZ (monozygotic) and DZ (dizygotic) twin pairs separately.

(4) To test two models: a common liabilities model and a random multiformity model, which captures some features of the gateway hypothesis.

METHOD

Sample

Data for these analyses come from male and female same-sex twin pairs from the Virginia Twin Registry. Twins were eligible for participation if they were born between 1940 and 1974 and were Caucasian. Respondents who agreed to participate were interviewed in the first wave of personal interviews. This included 72·8% of the eligible males and 91·9% of the eligible females. Zygosity was initially determined by standard questions and zygosity was later confirmed for a subsample of twins by molecular analyses. Three follow-up telephone interviews were completed in the females and one follow-up interview was conducted for the male twins. Data for the present analysis come from the second wave of interviews in the males and the fourth wave in the females and consists of 1196 male same-sex pairs and 934 female same-sex twin pairs, including MZ and DZ twin pairs. As approved by the institutional review board, all participants were informed about the objectives of the study prior to participation and informed consent was obtained prior to participation. Additional details regarding data collection and ascertainment are available elsewhere (Kendler *et al*. 1992, 2002).

Measures

Other illicit drug use was coded as a binary variable for lifetime use of cocaine, sedative, stimulants, opiates and hallucinogens. The combined category for the use of 'other illicit drug' includes use of cocaine, sedatives, stimulants, opiates or hallucinogens (but not including cannabis). The early cannabis use variable was created by ascribing a '1' to those individuals who reported use of cannabis before or at the age of 18 years and a '0' if the respondent was a non-user or used cannabis after the age of 18 years. For the categories of drugs that may be obtained legally (sedatives, stimulants and opiates) use was defined by any of the following criteria: (*a*) use without a prescription, (*b*) in greater amounts than prescribed, (*c*) more frequently than prescribed or (*d*) for reasons other than those for which it was prescribed. Abuse and dependence was assessed using DSM-IV criteria (APA, 1994). If the participant was diagnosed with abuse or dependence for cocaine,

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sedatives, stimulants, hallucinogens or opiates, they were diagnosed with abuse/dependence for 'any illicit drug'. Individuals who reported use of other illicit drugs before the age of 18 years were not included in the analysis.

In an attempt to replicate the methods used by Lynskey and colleagues, we used six covariates to adjust our odds ratios (ORs) as well as sex and zygosity. Regular alcohol use referred to drinking for at least once a month for 6 months or more, before or at the age of 18 years. Similarly, regular nicotine use reflects smokers who smoked regularly for at least a month, before or at the age of 18 years. The psychiatric disorders of Major Depression (MD), Generalized Anxiety Disorder (GAD) and Conduct Disorder (CD) were diagnosed using an adaptation of SCID (Spitzer *et al*. 1987) and the DSM-III-R criteria (APA, 1994). MD was based on a lifetime diagnosis, GAD utilized a lifetime report of a 1-month rather than a minimum 6-month duration of illness and CD was created based on the presence of three or more CD behaviors prior to the age of 18 years. Years of education corresponds to an interview item regarding the highest grade of school or college year completed.

We compared the Akaike Information Criterion (AIC) for models that imposed a linear or quadratic or logarithmic relationship, or spline functions that had knots at 12–25 years (SAS Institute, 1999) to determine early onset of cannabis use. The linear function provided the best fit to the data. The choice of 18 years to distinguish early and late onset is purely based on the median age of onset of cannabis use.

Statistical methods

PROC GENMOD in SAS was used to examine the association between early cannabis use and the use or abuse/dependence of other illicit drugs (SAS Institute, 1999). Data from all twin pairs was pooled and independent estimating equations (IEE) were employed to account for the clustering of twin data (SAS Institute, 1999). In an attempt to replicate the methods used by Lynskey *et al*. the ORs were adjusted for sex, years of education, CD, MD, GAD and regular alcohol and nicotine use.

We also used PROC GENMOD to assess the relationship between early cannabis use in one twin and subsequent other illicit drug use or abuse/dependence in the co-twin after controlling for the co-twin's early cannabis use. ORs were calculated separately for MZ and DZ twin pairs and the statistical difference between the MZ and DZ ORs was tested by interacting early cannabis use with zygosity. A similar interaction was employed to test for sex differences.

Our next step was to employ the discordant twin design to study the association between early cannabis use and other illicit drug use or abuse/dependence. Following the approach of Lynskey and colleagues, we selected twin pairs discordant for early cannabis use (Lynskey *et al*. 2003). The association between early cannabis use and use or abuse/dependence of other illicit drugs may be due to the following relationships: (i) early cannabis use has a causal influence on subsequent other illicit drug use or abuse/dependence or (ii) early cannabis use and other illicit drug use and abuse/dependence are related due to correlated genetic influences or (iii) a combination of causal and correlative influences are responsible for the relationship. To distinguish between these models, ORs from MZ and DZ twins were compared to each other and to the population ORs. If the association were purely causal, then early cannabis use would be strongly associated as a risk factor for subsequent use or abuse/dependence of other illicit drugs in the population and in the discordant MZ and DZ twin pairs. In other words, the extent of genetic overlap (100% in MZ and 50% in DZ twin pairs) would not influence the ORs. This definition of causality is fairly narrow and refers to the direct influence of early cannabis use on the use of other illicit drugs. On the other hand, if genetic factors common to early cannabis use and use or abuse/dependence of other illicit drugs were exclusively responsible for the association between the two drug categories, we would expect a different pattern of ORs. Early cannabis use would still be strongly associated with future other illicit drug use or abuse/dependence in the entire population. MZ twins who share all their genes and are discordant for early cannabis use would have ORs equal to 1·0. DZ twins, on the other hand only share 50% of their genes and would have ORs greater than 1·0 but less than the population OR. Fig. 1 presents a graphical description of a comparison of population, MZ and DZ ORs

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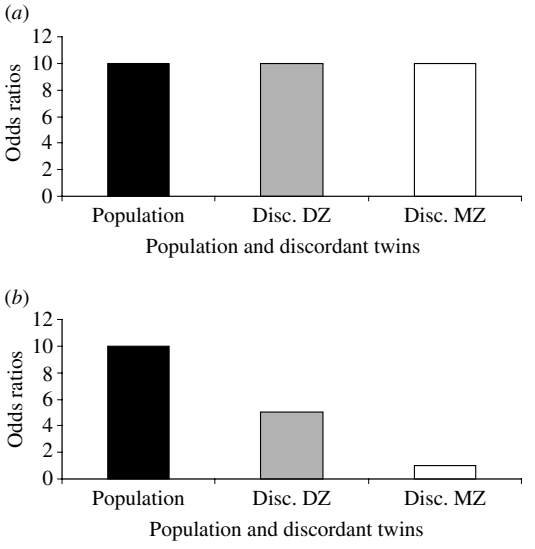

FIG. 1. Two types of associations between early cannabis use and subsequent use of other illicit drugs in the discordant twin design. (*a*) The pattern of odds ratios (ORs) seen if the relationship between early cannabis use and subsequent other illicit drug use is explained by causal influences alone. A fairly narrow definition of causality implied by this model. In this case, the MZ (□) and DZ (▩) discordant twin ORs (Disc. MZ and Disc. DZ respectively) are equal to each other and equal to the population (■) OR. Therefore, the risk of other illicit drug use is elevated, irrespective of genetic relationship. (*b*) The pattern of ORs that would be obtained if correlated genetic influences were solely responsible for the association between early cannabis use and the use of other illicit drugs. MZ twins who share all their genes have an OR (□) equal to unity while DZ twins who only share half their genes have an OR greater than unity (▩) but significantly lower than the population OR (■) where individuals are unrelated.

expected under a purely causal or a purely correlated liabilities model.

The discordant twin analyses were performed using conditional logistic regression in PROC PHREG in SAS. The ORs obtained from the conditional logistic regression model reflect the risk of other illicit drug use or abuse/dependence in an early cannabis using twin *versus* a non-user co-twin. The information in the analysis arises from the within-twin pair differences. In an attempt to replicate results presented by Lynskey and colleagues we first fit a model that pooled MZ and DZ twins. Covariates used for the population ORs were used for adjustment in the discordant twin design (Lynskey *et al.* 2003). The same analyses were performed by separating the MZ and DZ twins and controlling for sex. We assessed the statistical significance of different ORs in MZ and DZ discordant twin pairs by comparing a model that allowed for separate parameter estimates in MZ and DZ twins with a model that forced a single parameter estimate for both zygosities. Additionally, we tested for the effect of sex on this association.

We also used two models from the Neale–Kendler co-morbidity models to examine the association between early cannabis use and the subsequent use or abuse/dependence of other illicit drugs. To reduce the possible number of combinations of models and to maximize power, we only used the 'other illicit drug use' category (any illicit drug, except cannabis) for model-fitting. We tested three putative models to explain the relationship between early cannabis use and the use of 'other illicit drugs'. The first model fitted to the data was the correlated liability model where early cannabis use and the use of 'other illicit drugs' each have liabilities influenced by correlated genetic (A), shared environmental (C) and unique environmental (E) influences. We fitted a sub-model to the correlated liabilities model that only allowed for the unique environmental influences to be correlated (Re only). The correlated E model allows for twins to have correlated unique environmental influences alone and independent genetic and shared environmental factors. Additionally, we fitted a sub-model where only genetic (Ra) and shared environmental (Rc) cross-drug correlations were allowed and the correlation between unique environmental factors (Re) was constrained to zero.

The final model was the random multiformity of cannabis model, which captures some aspects of the gateway hypothesis. In this model, early cannabis use and use of 'other illicit drugs' is described by unique and independent liability distributions that are influenced by non-overlapping A, C and E. However, individuals above the threshold on the distribution for early cannabis use are users of cannabis and also at increased risk for using 'other illicit drug'. This increased risk is independent of the individual's liability to use 'other illicit drugs' itself. Thus, while some proportion of individuals use 'other illicit drugs' because they are above the threshold for 'other illicit drug' use, another proportion of individuals use 'other illicit drugs' only due to their prior early cannabis use. A significant limitation of this model is that it does not allow for correlations between A, C

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and E influencing each drug category. Although it would be extremely informative to test a model that combines aspects of the correlated liabilities model (with Ra, Rc and Re) and models causal paths, this model is not identified and therefore, cannot be tested.

Further descriptions and mathematical interpretations of the correlated liabilities and random multiformity model are available elsewhere (Neale & Kendler, 1995).

All structural equation models were fitted using Mx (Neale, 1990). Model-fit was compared using AIC, which is an index of fit and parsimony and is calculated by subtracting two times the degrees of freedom from the χ^2 fit. The model with the lowest AIC (largest negative) was the best-fitting model (Akaike, 1987; Williams, 1994).

RESULTS

Sample characteristics

This study utilized data from 2402 male and 1942 female same-sex twins. The mean age at the time of the interview was 35·5 years (range 20–58 years) for the males and 35·8 years (range 21–62 years) for the females. The mean of years of education reported by the twins was 13·6 and 14·3 years in the males and females respectively. Of these twins, 46·6% females and 52·9% males reported lifetime cannabis use. Of the cannabis users, 61·2% females and 64·5% males reported the early use of cannabis (i.e. 18 years or before). Forty-two per cent of the females and 62% of the males reported having used other illicit drugs.

Table 1 shows the ORs obtained when examining the association between early cannabis use and the use or abuse/dependence of other illicit drugs, within an individual. The ORs were calculated using the twin data as a population sample and unadjusted as well as covariate-adjusted ORs are presented. The association between early cannabis use and use and abuse/dependence of other illicit drugs, in the population, was robust. Early cannabis use was associated with other illicit drug use with an OR of 6·9 [95% confidence interval (CI) 5·8–8·1] and with other illicit drug abuse/dependence with an OR of 4·8 (95% CI 3·7–6·2).

The ORs presented in Table 2 refer to the extent to which twin 1's early cannabis use influenced subsequent other illicit drug use or abuse/dependence in twin 2, after controlling for early cannabis use in twin 2. The interaction of twin 2's other illicit drugs use with sex was

Table 1. *Within-person population odds ratios (ORs) and 95% confidence interval (CI) for risk for subsequent illicit drug use or abuse/dependence predicted by cannabis use before 18 years of age*

Drug	Unadjusted (95% CI)	Adjusted (95% CI)
Use		
Any illicit	9·8 (8·4–11·5)	6·9 (5·8–8·1)
Cocaine	9·9 (8·2–11·9)	6·8 (5·6–8·3)
Sedatives	6·9 (5·5–8·5)	4·0 (3·2–5·1)
Stimulants	8·9 (7·4–10·7)	5·8 (4·7–7·1)
Hallucinogens	12·3 (9·8–15·4)	8·0 (6·3–10·2)
Opiates	7·1 (5·2–9·6)	3·8 (2·7–5·4)
Abuse/dependence		
Any illicit	7·7 (6·1–9·6)	4·8 (3·7–6·2)
Cannabis	13·2 (10·6–16·4)	8·4 (6·6–10·5)
Cocaine	10·6 (7·3–15·4)	5·6 (4·0–8·9)
Sedatives	7·4 (4·7–11·8)	5·2 (3·3–8·2)
Stimulants	7·2 (5·4–9·6)	4·7 (3·4–6·5)
Hallucinogens	14·7 (8·6–24·9)	7·5 (3·9–14·2)
Opiates	4·7 (2·7–8·2)	2·6 (1·5–4·6)
Alcohol dependence	3·2 (2·7–3·7)	8·4 (6·6–10·5)

Table 2. *Odds ratios (ORs) and 95% confidence interval (CI) where twin 1's cannabis use before 18 years predicts twin 2's illicit drug use and abuse/dependence after controlling for twin 2's own early cannabis use. Results based on logistic regression controlling for sex*

Drug	MZ OR (95% CI)	DZ OR (95% CI)	Statistical significance of MZ and DZ ORs*
Use			
Any illicit	3·2 (2·5–4·0)	1·7 (1·3–2·2)	0·0003
Cocaine	3·6 (2·7–4·7)	1·8 (1·3–2·4)	0·0011
Sedatives	2·6 (1·8–3·8)	1·5 (1·0–2·1)	0·0170
Stimulants	2·6 (2·0–3·4)	1·8 (1·3–2·5)	0·0046
Hallucinogens	3·0 (2·3–4·0)	1·7 (1·3–2·4)	0·0067
Opiates	3·6 (2·2–5·8)	1·6 (1·0–2·6)	0·0084
Abuse/dependence			
Any illicit	2·9 (1·2–4·1)	1·2 (0·8–1·7)	0·0001
Cannabis	2·8 (2·0–3·7)	1·7 (1·2–2·4)	0·0037
Cocaine	3·0 (1·7–5·0)	1·6 (0·9–2·6)	0·0648
Sedatives	2·3 (1·3–4·3)	1·4 (0·8–2·5)	0·1284
Stimulants	2·7 (1·7–4·2)	1·3 (0·9–2·0)	0·0044
Hallucinogens	5·1 (2·2–11·5)	1·2 (0·6–2·6)	0·0005
Opiates	1·8 (0·8–4·2)	2·7 (1·2–6·2)	0·7200
Alcohol dependence	1·5 (1·2–1·9)	1·0 (0·8–1·4)	0·0280

* Analyses adjusted for sex. Values presented are two-tailed *p* values.

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Table 3. *Odds ratios (ORs) for MZ and DZ twins in the discordant twin design. ORs reflect risk of subsequent other illicit drug use or abuse/dependence in an early cannabis user twin versus the non-user co-twin*

Drug	DZ OR (95% CI)	MZ OR (95% CI)	Difference between MZ and DZ OR*
Use			
Any	5·8 (3·1–8·7)	2·6 (1·5–4·4)	0·012
Cocaine	4·8 (2·2–7·4)	2·2 (1·2–4·0)	0·096
Sedatives	3·8 (1·8–7·9)	1·9 (1·0–4·0)	0·155
Stimulants	4·1 (2·1–8·0)	3·1 (1·7–5·9)	0·060
Hallucinogens	7·9 (3·4–18·6)	6·8 (2·4–19·3)	0·788
Opiate	2·8 (1·1–7·2)	1·2 (0·4–3·3)	0·442
Abuse/dependence			
Any	5·8 (2·6–13·0)	1·9 (0·8–4·3)	0·008
Cannabis	4·7 (2·5–8·9)	9·2 (3·3–25·8)	—
Cocaine	4·9 (1·7–14·3)	3·2 (0·9–11·9)	0·542
Sedatives	3·7 (1·0–13·1)	5·5 (0·7–46·6)	0·692
Stimulants	1·7 (0·7–4·4)	5·6 (1·9–16·2)	0·014
Hallucinogens	3·4 (1·0–12·5)	—	—
Opiates	0·8 (0·4–3·4)	3·0 (0·3–28·0)	0·215
Alcohol dependence	2·8 (1·7–4·7)	2·2 (1·3–3·7)	—

* Values presented are two-tailed p values.

not significant ($p > 0{\cdot}1$), which allowed us to pool male and female twins for further analyses. The ORs for the association between early cannabis use and use and abuse/dependence of other illicit drugs were strong and significant. With the exception of abuse/dependence of sedatives and opiates, the DZ ORs were consistently lower than the MZ ORs. Overall, the ORs in MZ twins were 1·5–4·0 times greater than the ORs in DZ twins and these differences were statistically significant.

Males and females were pooled for the discordant twin analyses. However, MZ and DZ twin pairs were analyzed separately. Even after adjusting for potential covariates, there was a significant increase in risk of other illicit drug use and abuse/dependence in early cannabis users compared to their non-user co-twins. Results for the pooled sample are available upon request. Table 3 presents ORs for the discordant twin design, separately for MZ and DZ twin pairs. The difference between the MZ and DZ ORs was significant for other illicit drug use and other illicit drug abuse/dependence but not for the individual drugs.

Fig. 2 depicts our results for the ORs observed in the discordant twin analyses. The

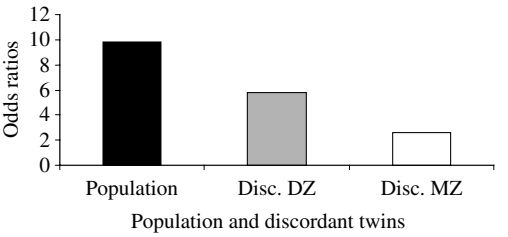

FIG. 2. The pattern of MZ and DZ odds ratios (ORs) observed in our sample of discordant twin pairs from the Virgnia Twin Registry. The ORs presented in the diagram depict ORs for early cannabis use and subsequent use of other illicit drugs. Overall, the pattern of ORs is very similar to the pattern of ORs presented in the correlated genetic factors model in panel (*b*) of Fig. 1. The MZ OR (□) is lower than the DZ OR (▨), which is lower than the population OR (■). However, unlike the expected pattern in Fig. 1, the MZ OR is greater than 1·0. This suggests that the relationship between early cannabis use and other illicit drugs is partly due to correlated genetic factors and partly due to causal influences.

pattern was similar to the correlated genetic model in Fig. 1. The population OR was significantly higher than the discordant twin ORs. Within the discordant twin design, the DZ OR for early cannabis use predicting other illicit drug use or abuse/dependence was significantly greater than the MZ OR but considerably lower than the population OR. However, our observed pattern of ORs differs from the pattern predicted by a model where correlated genetic factors alone explain the relationship between the two drug categories in one important way: the MZ OR was significantly greater than unity.

The model-fitting procedure provided some interesting insights as well (Table 4). The best-fitting correlated liabilities model in males and females allowed for genetic, shared and unique environmental correlations across early cannabis use and use of 'other illicit drugs'. The correlation between the genetic factors (Ra) was substantial (0·91 in males and 1·0 in females) while the shared environmental factors (Rc) were correlated between 0·68–1·00. The unique environmental factors (Re) showed low correlations with greater evidence for drug-specific environmental influences. The proportion of the total covariance due to genetic factors was 46% in males and 53% in females. Correlated unique environmental influences contribute to 13% and 10% of the total covariance in males and females respectively, with the remaining covariance accounted for by shared environmental influences. Furthermore, a submodel where Re

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Table 4. *Model-fit and parameter estimates for model-fitting procedure*

Model	AIC	Early cannabis use			Other illicit drug use			Ra	Rc	Re	Total covariance	% A	% C	% E
		a^2	c^2	e^2	a^2	c^2	e^2							
Males														
Correlated liabilities	−7·0	0·23	0·50	0·27	0·57	0·17	0·26	0·91	1·00	0·34	0·71	46	41	13
Correlated E only	265·6	0·05	0·21	0·74	0·23	0·00	0·77	—	—	0·87	—	—	—	—
Random multiformity model	77·5	0·16	0·52	0·32	0·69	0·00	0·31	—	—	—	—	—	—	—
Females														
Correlated liabilities	−7·7	0·44	0·36	0·20	0·30	0·39	0·31	1·00	0·68	0·26	0·68	53	37	10
Correlated E only	210·8	0·05	0·34	0·61	0·00	0·24	0·76	—	—	0·81	—	—	—	—
Random multiformity model	41·9	0·40	0·38	0·22	0·00	0·64	0·36	—	—	—	—	—	—	—

a^2, Additive genetic influence; c^2, shared environmental influence; e^2, unique environmental influence.

Ra, Genetic correlation between early cannabis use and use of any illicit drug; Rc, shared environmental correlation between early cannabis use and use of any illicit drug; Re, unique environmental correlation between early cannabis use and use of any illicit drug.

% A, % C and % E refer to the percentage of the total covariance due to additive genetic, shared environmental and unique environmental factors.

The best-fitting model is highlighted in gray.

was set to zero led to a significant increase in AIC ($AIC_{males} = 2{\cdot}24$, $AIC_{females} = -1{\cdot}27$). This increase in AIC indicated that while the unique environmental influences were only modestly correlated, their influence on early cannabis use and use of 'other illicit drugs' via a correlated pathway could not be ignored. The model with correlations only between unique environmental factors (correlated E model) fitted poorly. Finally, the random multiformity of cannabis model did not fit the data well.

DISCUSSION

Cannabis is the most commonly used illicit psychoactive drug in the US population and has been proposed as a gateway drug (Kandel & Yamaguchi, 1993; Golub & Johnson, 1994; Kandel, 2003). A prior twin study provides evidence for the causal influence of early cannabis use on the use and abuse/dependence of other illicit drugs (Lynskey *et al*. 2003). The primary goal of our study was to elucidate the relationship between early cannabis use and use and abuse/dependence of other illicit drugs in another genetically informative sample. We used four related methods to study the association between the two drug categories beginning with an assessment of the within-person association between early cannabis use and use and abuse/dependence of other illicit drugs in the entire twin sample. This was followed by a test for cross-twin prediction of risk of other illicit drug use and abuse/dependence from the co-twin's early cannabis use. Next, we used the discordant twin design to identify the nature of the association between early cannabis use and other illicit drug use and abuse/dependence. Finally, we examined models that test the impact of correlated liabilities or random multiformity on the relationship between the two drug categories.

We documented a strong and significant association between early cannabis use and use and abuse/dependence of other illicit drugs. The cross-twin analyses, showed that early cannabis use in one twin was a significant predictor of other illicit drug use and abuse/dependence in the co-twin even after controlling for the co-twin's own early cannabis use. Furthermore, the cross-twin prediction was substantially stronger in MZ twins who share all their genes than in DZ twin pairs, who share only 50% of their genes. This suggested that genetic factors that influence both early cannabis use and other illicit drug use and abuse/dependence may be partly responsible for the association between the two drug categories.

The discordant twin analyses yielded a very informative pattern of MZ–DZ ORs. Discordant

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DZ twins had ORs significantly greater than discordant MZ twins but lower than the population ORs. The MZ ORs were greater than 1·0 and this suggests a true causal influence of early cannabis use on the use and abuse/dependence of other illicit drugs. However, this elevation of MZ ORs could also be due to correlated environments. Overall, our results suggest that a significant proportion of the relationship between early cannabis use and subsequent use or abuse/dependence of other illicit drugs is due to correlated genetic and environmental factors but we cannot rule out the role of direct causal influences in this relationship.

Issues of causality pose a challenge in the study of genetically informative data. Analysis of data from discordant twin pairs cannot distinguish a truly causal model from a model where the overlap of unique environmental influences across the two drug categories leads to uniformly elevated ORs. For example, imagine that a certain environmental factor, such as childhood head trauma, causes early cannabis use and subsequent use of other illicit drugs. Now, consider an MZ twin pair where one member suffers the head trauma but the other member of the twin pair does not. As a consequence of the head trauma, the twin with the trauma is predisposed to cannabis use before the age of 18 years as well as other illicit drug use. The member of the twin pair that did not experience the trauma uses neither cannabis nor other illicit drugs. Even though the twins share all their genetic factors, one member of the twin pair did not experience the environmental factor – the head trauma and hence, this MZ twin pair is discordant for early cannabis use. However, when the early cannabis user twin is compared to the non-user co-twin for subsequent other illicit drug use, it would seem like the cannabis-using twin has a greater risk for subsequent other illicit drug use than the non-user twin. However, the reason for this increased risk is because the cannabis-using twin experienced the head trauma, which influenced both his early cannabis and other illicit drug use (or a common liability to illicit drug use) and not because early cannabis use has a causal impact on subsequent other illicit drug use. This correlated environmental influence cannot be discriminated from a true causal effect within the discordant twin design.

However, it is also possible that the elevation in the MZ OR is due to the causal influence of early cannabis use on the subsequent use or abuse/dependence of other illicit drugs. Theoretically, the only method that could truly assess the causal impact of early cannabis use on later other illicit drug use is a prospective study that measures environmental factors. Such a study would allow an estimation of common and specific environmental influences on each drug and control for them. However, choice of which environmental factors to measure, how to measure them and the possibility that they are elicited or selected by certain individuals are serious obstacles to such a study.

Overall, the complementary techniques employed in this study suggest a robust association between early cannabis use and other illicit drug use and abuse/dependence. There was also some evidence for the causal influence of early cannabis use on subsequent use or abuse/dependence of other illicit drugs and this causal effect was indistinguishable for the influence of correlated environmental factors. Some of earliest evidence for the gateway suggested that age of onset of cannabis had a significant causal impact on later illicit drug use (O'Donnell & Clayton, 1982; Voss & Clayton, 1987; Graham *et al.* 1991; Kandel *et al.* 1992; Kandel & Yamaguchi, 1993; Hawkins *et al.* 1997). Morral and colleagues reported that use of cannabis before 15 years of age conferred a 1·60 times greater risk for other illicit drug use than if initiation was after 15 years (Morral *et al.* 2002*a*). Furthermore, another study reported an elevated hazard ratio of 140·0 in users of cannabis for future use of other illicit drugs (Fergusson & Horwood, 2000). While each of these studies commented on the increased risk of using other illicit drugs in early users of cannabis, they did not formally comment on the causal nature of the association.

We are unaware of any epidemiological analyses that directly imply that the influence of cannabis use on subsequent use of other illicit drugs is causal (Kandel, 2003). One reason for this is the inability to determine causality independent of correlated environments. While animal models have provided some evidence for the causal impact of cannabis use, these controlled experiments are impossible in humans (Tanda *et al.* 1997; Cadoni *et al.* 2001; Lamarque *et al.*

2001). Twin studies allow us to control for genetic background when assessing causal inference. A recent report presented significant evidence for elevated ORs in co-twins of early cannabis user twins (OR 2·1–5·2) (Lynskey *et al.* 2003). The analyses by Lynskey *et al.* suggested a 2·1–5·2 times higher odds of other illicit drug use and abuse/dependence in early cannabis users than non-users. Our results show similar ORs but present an alternative explanation for the elevated ORs in the discordant twin design. Also, the methods used by Lynskey *et al.* were somewhat different from our approach. First, Lynskey *et al.* did not assess ORs in MZ and DZ twin pairs separately. According to their discordant twin analyses, an interaction with zygosity was not significant and MZ and DZ twins could be pooled within the discordant twin design. We, on the other hand, noted significantly higher DZ *versus* MZ ORs in our discordant twin design. This divergence in the results may reflect true differences between drug habits and association between illicit drugs in the United States and Australian populations. Secondly, Lynskey and colleagues did not employ a model-fitting approach nor did they attempt to distinguish between true causality and correlated environments. While our model-fitting methods are limited by certain assumptions (e.g. no gene–environment correlations, assortative mating) and are unable to test certain key models, they are complementary to the discordant twin design and shed further light on the complex process of poly-drug use and misuse.

In our data, the association between early cannabis use and other illicit drug use or abuse/dependence was partly due to the correlated nature of the factors that influence these drugs. Furthermore, the correlated genetic factors account for 46% and 53% of the total covariance in males and females respectively. This common liability model has been supported by some epidemiological analyses (MacCoun, 1998; Morral *et al.* 2002*a*, *b*). A simulation study by Morral and colleagues showed that both sequencing and association can be explained by a common liability model where drug use propensity drives both processes without imposing a causal pathway from cannabis use to subsequent use of other illicit drugs (Morral *et al.* 2002*a*). Genetic studies can partition these common factors into genes and environment. Most genetic studies provide evidence for a high correlation of genetic factors (van den Bree *et al.* 1998; Tsuang *et al.* 2001; Kendler *et al.* 2003). A study by Tsuang and colleagues compared a liability-based gateway to a common pathway model and rejected the gateway model (Tsuang *et al.* 1998). Our random multiformity of cannabis model, which measures the impact of early cannabis use *per se*, was also rejected. A theoretically superior model that examines the gateway effect would include the strong correlations between genetic and environmental factors that we observe, plus causal pathways. While such a model is conceptually more informative, it is not identified. Therefore, given the scope of the present data and the techniques available to us, we can only claim that strong genetic and environmental correlations are partly responsible for the relationship between cannabis and other illicit drugs. While there is some evidence for causal influences, our results suggest that these causal influences cannot explain all the association between early cannabis use and the subsequent use and abuse/dependence of other illicit drugs.

In conclusion, the relationship between early cannabis use and use and abuse/dependence of other illicit drugs is strongly influenced by correlated genetic and environmental factors. A proportion of these environmental factors, which may be the effect of deviant peer groups that allow opportunity for exposure to all kinds of illicit drugs (Dishion & Owen, 2002; Heim *et al.* 2002; Wagner & Anthony, 2002) are common to early cannabis use and use and abuse/dependence of other illicit drugs. These common factors may be one possible explanation for the relationship between the two drug categories (Lynskey *et al.* 2003). On the other hand, it is possible that early cannabis use has a true causal impact on other illicit drug use and abuse/dependence. Future studies need to consider both these sources (correlated and causal factors) when examining the association between cannabis and other illicit drugs.

Limitations

The findings in this paper should be viewed with the following limitations in mind:

(1) These results depend on the validity of retrospectively reported data. There may be some recall bias or telescoping when reporting use of cannabis, age of first use and use and

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symptoms of abuse/dependence of other illicit drugs. While we only have data on the illicit drugs from one wave of interviews, short-term test–retest reliability measures ($n=172$ twin pairs measured after 4 weeks of primary interview) are available on a subset of the twin pairs. Drug use was assessed with very high test–retest reliability ($r=0{\cdot}98$ for cannabis and $r>0{\cdot}90$ for other illicit drugs). Abuse/dependence was diagnosed with fair reliability with intra-class correlations $r>0{\cdot}80$. Additionally, the age of onset of first cannabis use was reported with a very high reliability ($r=0{\cdot}91$). Therefore, it is unlikely that the findings in this analysis have been significantly impacted by recall bias.

(2) These analyses pool non-users of cannabis with those who initiated cannabis use after the age of 18 years. We performed the population regression and discordant twin analyses with a different definition of early cannabis use where only users of cannabis were included in the analyses. Early cannabis use was defined as a binary variable where users initiated cannabis use before or at the age of 18 years and non-users initiated cannabis use after 18 years (non-users not included). This analysis found ORs that were fairly low and we had limited ability to distinguish discordant MZ and DZ ORs. However, the pooled ORs for early cannabis use predicting other illicit drug use was significantly greater than unity for all drugs except cocaine and sedatives. The magnitude of the ORs may reflect a true lack of association but it is more likely that the poor ability to discriminate the ORs is due to the extremely reduced sample size that results from eliminating 50% of the dataset by ignoring the non-users. Results are available upon request.

(3) We used drug use as a binary variable assessing lifetime use of cannabis and other illicit drugs. While age of onset data was utilized to code the early cannabis use variable, we did not employ the frequency of use data that could potentially distinguish experimental users from regular users.

(4) As noted in the text, we employ a fairly narrow definition of causality for the discordant twin design. Due to the nature of retrospective report data, certain assumptions were made during the twin analyses and therefore, true measures of causality are not within the scope of this study.

(5) This study utilizes information from Caucasian twin pairs and these results may not apply to other ethnicities or to other socioeconomic strata.

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DECLARATION OF INTEREST

None.

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