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Genetic and environmental contributions to cannabis dependence in a national young adult twin sample

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ABSTRACT

Background. This paper examines genetic and environmental contributions to risk of cannabis dependence.

Method. Symptoms of cannabis dependence and measures of social, family and individual risk factors were assessed in a sample of 6265 young adult male and female Australian twins born 1964–1971.

Results. Symptoms of cannabis dependence were common: 11·0% of sample (15·1% of men and 7·8% of women) reported two or more symptoms of dependence. Correlates of cannabis dependence included educational attainment, exposure to parental conflict, sexual abuse, major depression, social anxiety and childhood conduct disorder. However, even after control for the effects of these factors, there was evidence of significant genetic effects on risk of cannabis dependence. Standard genetic modelling indicated that 44·7% (95% CI = 15–72·2) of the variance in liability to cannabis dependence could be accounted for by genetic factors, 20·1% (95% CI = 0–43·6) could be attributed to shared environment factors and 35·3% (95% CI = 26·4–45·7) could be attributed to non-shared environmental factors. However, while there was no evidence of significant gender differences in the magnitude of genetic and environmental influences, a model which assumed both genetic and shared environmental influences on risks of cannabis dependence among men and shared environmental but no genetic influences among women provided an equally good fit to the data.

Conclusions. There was consistent evidence that genetic risk factors are important determinants of risk of cannabis dependence among men. However, it remains uncertain whether there are genetic influences on liability to cannabis dependence among women.

INTRODUCTION

There is now convincing evidence of a genetic component to risks of both nicotine dependence (Kendler *et al.* 1999; True *et al.* 1999) and alcohol dependence (Heath, 1995; Heath *et al.* 1997; Schuckit, 1999; True *et al.* 1999). By comparison, there has been relatively less research conducted into the extent to which risks of cannabis use and dependence may be influenced by genetic factors. Nonetheless, a small number of recent studies have examined the genetic liability to cannabis dependence and related problems. For example, in a study of 967 female same-sex twin pairs, Kendler & Prescott (1998) reported that genetic factors accounted for 40% of the variance in cannabis use, 79% of the variance in heavy cannabis use, 72% of the

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variance in cannabis abuse and 62% of the liability to cannabis dependence. Similar results were reported by Kendler *et al.* (2000*a*) for a sample of 1198 male twin pairs. Estimates of heritability were 33% for use, 84% for heavy use, 74% for abuse and 58% for dependence. While there were significant shared environment effects on cannabis use in both female and male samples, there were no significant shared environmental effects on risks of heavy use, abuse or dependence.

One feature of these results is that it appears that genetic factors may be relatively more influential in the aetiology of cannabis misuse or dependence than they are in the aetiology of earlier stages of cannabis use, such as experimentation. This suggestion has also been supported by a study of cannabis use and abuse in a treatment sample, which found that genetic factors were relatively less important determinants of use than of abuse or dependence (van den Bree *et al.* 1998) and by the results of a recent study of adolescent twins which highlighted the relative importance of shared environmental factors in the aetiology of early experimentation and drug use (Maes *et al.* 1999).

Although research indicates that a substantial component of the liability to cannabis dependence can be attributed to genetic factors, there are a number of features of this association that remain to be determined.

Gender differences

The first concerns the extent to which there may be gender differences in the heritability of cannabis use or dependence. While the studies reviewed above suggest that the heritability of cannabis dependence is likely to be similar for males and females, the majority of these studies have studied twins of only one gender. To explore fully gender differences in the heritability of cannabis dependence it is necessary to conduct within-study comparisons of heritability estimates between males and females. Additionally, the inclusion of unlike-sex twin pairs is necessary to provide a test of whether the same or different risk factors (either genetic or environmental) influence outcomes for both genders (Neale & Cardon, 1992). If there are large gender differences in the relative contributions of genetic and environmental influences to risk of cannabis use or dependence, or risk factors that are gender specific, concordance rates should be extremely low in unlike-sex twin pairs.

The importance of considering potential gender differences in genetic influences on cannabis dependence has been underlined by the results of a recent study suggesting that genetic factors may play a relatively more influential role in the aetiology of cannabis and other drug dependence among males than among females (van den Bree *et al.* 1998). Specifically, while they estimated significant genetic effects on risks of sedative and opiate abuse/dependence among men (58% and 57% of the variance respectively), there was no evidence of genetic effects on these outcomes among women. While they reported significant genetic effects on risks of cannabis dependence among women (53%) this estimate was somewhat lower than the estimate for men (68%). Estimates of the heritability of any drug abuse/dependence were substantially higher for males (79%) than for females (47%).

Mediators of genetic influence

There has been less research exploring the developmental mechanisms and pathways for these genetic influences. Existing research has explored this issue with respect to alcohol dependence (e.g. Heath *et al.* 1997) but there appears to have been only limited previous research exploring potential pathways underlying cannabis dependence. Nonetheless, there are a number of factors that may mediate genetic or shared environmental influences on risk of cannabis dependence. These include social disadvantage, family dysfunction, exposure to childhood sexual abuse, early childhood conduct disorder and other psychiatric disorders.

Research has consistently shown that these and similar factors are associated with increased risks for developing substance use problems (Hawkins *et al.* 1992) and, additionally, there is evidence that rates of exposure to these factors may be elevated in families susceptible to substance use disorders. For example, there is considerable research evidence that childhood conduct disorder is both a risk factor for the development of cannabis and other drug dependence (Robins & Price, 1991; Fergusson &

Lynskey, 1998) and is itself heritable (Eaves *et al.* 1997; Slutske *et al.* 1998; Rutter *et al.* 1999).

Study aims

Against this general background, the aims of this study were to document the relative contributions of genetic and shared environment influences on risk of developing cannabis dependence. Specific aims of the study were to: (1) document the extent to which risk of cannabis dependence is heritable among males and females and the extent to which the heritability of cannabis dependence may differ by gender; (2) explore potential factors, including sociodemographic factors, family environment, exposure to early abuse and childhood conduct disorder, which may mediate genetic or environmental influences on risk of cannabis dependence; and (3) compare the extent to which genetic, shared environment and non-shared environmental factors contribute to variance in lifetime cannabis use, heavy use and dependence. These issues are examined using a large sample of 6265 male and female Australian twins born during the period 1964–1971.

METHOD

Sample

Interviewees were members of the young adult cohort of the Australian Twin Register, a volunteer twin panel who were born between 1964–1971. Nearly all were first registered with the panel between 1980 and 1982 by their parents in response to approaches either through Australian school systems or via mass media appeals. Twins were first contacted as adults in 1989 by means of a mailed questionnaire. The data presented in this report are derived from responses to a telephone interview conducted by lay interviewers during the period 1996–2000. Informed consent was obtained from participants prior to administering the interviews, as approved by the institutional review boards of Washington University-St Louis and the Queensland Institute of Medical Research. Assignment for interview assessment was not dependent upon participation in the earlier questionnaire study.

Sample size and responses rates

The initial panel recruited in 1980–82 comprised 4262 twin pairs. Of these, 5·9% of pairs could not be located even after extensive efforts to locate family members. Diagnostic interviews were conducted during 1996–2000 with 6265 individuals, which comprised 78·1% of the remaining 8020 twins. Allowing for individuals who could not be located, who were deceased, incapacitated or otherwise unable to complete a telephone interview, or who were not assigned for interview by the end of the study, the individual response rate increases to 84·2%. The final sample included both twins from 1186 monozygotic (MZ) pairs (699 female and 487 male pairs), 895 same-sex dizygotic (DZ) twin pairs (508 female and 387 male pairs) and 655 unlike-sex pairs. Data from 753 single twins (377 females and 376 males) were also included in the analyses, yielding an overall sample size of 3445 women and 2779 men. Excluded from these totals are a small number of individuals who either did not complete the telephone interview ($N = 32$) or who refused to answer the drug section ($N = 9$). The median age at assessment of respondents was 30 (range = 24–36).

Assessments

A structured diagnostic interview that had been designed for genetic studies on alcoholism, the SSAGA (Bucholz *et al.* 1994) was adapted for telephone use, and updated for DSM-IV diagnostic criteria (American Psychiatric Association, 1994). Diagnostic assessments in the adapted SSAGA (SSAGA-OZ) included lifetime history of cannabis dependence, major depression and childhood conduct disorder as well as a non-diagnostic assessment of history of social anxiety. The interview schedule also included assessments of sociodemographic factors, childhood family environment and experiencing sexual abuse during childhood (Nelson *et al.* 2002). Interviews were conducted by lay interviewers who received extensive training in structured interviewing. Subject to respondent consent, all interviews were audio-taped for quality control. Separate interviewers interviewed each member of a twin pair, so that interviews were conducted without prior knowl-

edge of the history of the twin or his or her co-twin or family members.

Measures

Cannabis use, heavy use and dependence

Three measures of cannabis use were included in the analyses, as follows.

(*i*) *Lifetime use*

Lifetime use was based on respondent report of ever having used cannabis.

(*ii*) *Heavy use*

Respondents who reported using cannabis on at least three occasions a week were classified as heavy users. This definition approximated that used by previous researchers. Specifically, Kendler & Prescott (1998) defined heavy cannabis use as using cannabis on more than 10 occasions per month. Thus, our measure is not identical to and may, in fact, be more stringent than that used by Kendler & Prescott (1998).

(*iii*) *Cannabis dependence*

Individuals reporting using cannabis on at least a monthly basis were asked a further series of questions concerning the extent to which they may have experienced a range of symptoms of cannabis dependence. Due to time constraints on the interview, for which illicit drug dependence was not a primary focus, respondents were not asked all dependence criteria but the interview was, instead, restricted to the following criteria: using cannabis more frequently or for longer periods than intended; needing larger amounts to achieve an effect (tolerance); continued use of cannabis despite use causing emotional problems; and, recurrent desire to cut down on use. Individuals who reported two or more of these symptoms were considered to be cannabis dependent.

As this measure did not provide formal DSM-IV diagnostic criteria we conducted a series of analyses examining the sensitivity and specificity of our modified criteria against full DSM-IV criteria using two data sets: the Australian National Survey of Mental Health and Well-being (NSMHWB: Hall *et al.* 1999), which provided 12 month DSM-IV criteria; and the United States National Comorbidity Survey (NCS; Kessler *et al.* 1994), which provided lifetime DSM-III-R diagnostic criteria. These analyses indicated that our modified criteria had both excellent sensitivity and specificity. In the NSMHWB the sensitivity of our modified criteria was 96·7% and specificity (among cannabis users) was 94·6%. Similarly, in the NCS the sensitivity and specificity for lifetime criteria were 88·8% and 98·5% respectively. We also assessed the agreement between our modified criteria and DSM criteria using kappa. This analysis confirmed a high level of agreement between the two sets of criteria in both the NCS ($\kappa = 0{\cdot}85$) and NSMHWB ($\kappa = 0{\cdot}89$). Thus, while we did not assess full DSM diagnostic criteria the results of these analyses provide reassurance that our modified criteria provided a valid measure of cannabis dependence.

Sociodemographic, family and individual factors

Potential covariates were selected for inclusion in analyses based on their availability within the data-set and on a consideration of the factors that have previously been identified in the literature as being associated with increased risks of substance use and substance use problems.

Sociodemographic variables

Information on a range of sociodemographic factors was collected. The variables used in the present analysis included: (1) gender; (2) age at interview in years; (3) educational level. Education was collapsed to a four-point scale: (*i*) early school leavers with no further educational training or apprenticeship; (*ii*) at least some high school, a diploma, trade certificate or apprenticeship; (*iii*) technical or teachers' college; or (*iv*) university education or higher.

Family background

Parental separation

Respondents were asked whether they had been reared by both their natural parents up to the age 16 years.

Parental conflict

Those reared by both parents for at least part of the time between the ages of 6 and 13 were asked to describe the frequency of fights and arguments and the level of tension between their parents.

Those reporting frequent parental fights or arguments were classified as having been exposed to high levels of parental conflict.

Sexual abuse

Respondents were also asked a series of questions concerning their exposure to unwanted sexual contact, sexual molestation or rape. A composite measure was constructed which classified respondents who reported any such experiences before the age of 18 years as having a history of childhood sexual abuse. Details of this measure have been reported elsewhere (Nelson *et al*. 2002).

Psychiatric disorders

DSM-IV (American Psychiatric Association, 1994) conduct disorder and major depression were assessed using the modified SSAGA and diagnoses were assigned by computer algorithm. A non-diagnostic measure of social anxiety was also defined.

Similarity of early environment

A series of self-report measures of the similarity of childhood environment were available to test the equal environment assumption. These items were: (*a*) 'When you and your twin were 6–13, how often did you share the same friends?'; (*b*) 'How often did you dress alike?'; (*c*) 'In primary school, how often were you in the same classes at school?'; (*d*) 'In high school, how often were you in the same classes at school?'. Each of these items was rated on a five-point scale (always/usually/sometimes/rarely/never) and a composite index of similarity of environment was constructed for each twin pair by: (1) dichotomizing each of the above four measures so that 'always' and 'usually' responses were code as one and remaining responses as zero; (2) twin pairs who had similar ratings on each question were code as one for that item while those with discordant ratings, implying that at least one twin perceived there to be differences in early experiences, were coded zero; (3) measures of concordance for each of the items were summed to create a single scale (range 0–4) reflecting similarity of childhood environments; and (4) to divide the sample into approximately equal halves the sample was split so that twin pairs who agreed on all four items were classified as experiencing equal childhood environments (40% of the sample) while remaining sample members were classified as having dissimilar childhood environments.

Statistical analyses

Descriptive analyses

Estimates of lifetime prevalence of modified cannabis dependence were computed for the entire sample of males and females. Estimates of twin pair probandwise concordance, which measure the probability that the co-twin of a twin with cannabis dependence will also have a history of cannabis dependence, were also calculated. Probandwise concordance rates were estimated using the traditional formula:

$$2C/(2C+D),$$

where, C is the number of concordant cannabis dependent pairs and D the number of discordant pairs. The statistical software package Mx (Neale *et al*. 1999) was used to obtain 95% confidence intervals for prevalence and probandwise concordance rates, corrected for the non-independence of observations on twin pairs (Neale & Miller, 1997).

We tested the statistical significance of the association between cannabis dependence and co-twin's history of cannabis dependence controlling for sociodemographic variables using logistic regression. For each gender, five dummy variables were created to code co-twin's zygosity and cannabis dependence status. Analyses were then extended by the inclusion of measures of family environment, sexual abuse and other psychiatric disorders as predictor variables in stepwise regression analysis, forcing in significant sociodemographic variables. Logistic regression analyses were implemented in STATA (Stata Corp, 1999) using Huber–White robust variance estimation to obtain 95% confidence intervals adjusted for the non-independence of observations on twin pairs.

To test for residual genetic or shared environmental influences on risks of cannabis dependence that were not mediated by effects on sociodemographic, family or related variables, we examined the significance of the residual association between the respondent's and co-twin's cannabis dependence when these former variables were controlled. Any remaining association between cannabis dependence and co-twin's cannabis dependence after sociodemo-

graphic and other covariates were controlled for would indicate that familial effects were still important for the development of cannabis dependence. A test of the equality of odds ratios for MZ *versus* DZ same-sex pairs was conducted using the Wald χ^2, adjusted for non-independence (Stata Corp, 1999), to test for genetic effects. In the univariate case this test will give results that are almost identical to the likelihood-ratio χ^2 test obtained by fitting an ACE model to contingency tables (Heath *et al.* 1998).

Genetic model-fitting

As a final step, standard genetic model-fitting procedures (Eaves *et al.* 1978; Kendler *et al.* 1986; Neale *et al.* 1999) were used to obtain estimates of the proportion of the total variance in risk of cannabis dependence that could be explained by additive genetic factors, shared and non-shared environmental influences. Estimates were obtained under a multifactorial threshold model, which assumed that a continuous normal liability distribution underlies the observed binary distribution of cannabis dependence, and that the distribution of twin pairs for this latent liability variable was bivariate normal. These are the standard assumptions used in the estimation of tetrachoric and polychoric correlations (Tallis, 1962, Joreskog & Sorbom, 1993).

Models were fitted to the observed summary statistics for each zygosity group i.e. the numbers of concordant cannabis dependent, discordant and concordant unaffected twin pairs, and of cannabis dependent and unaffected singleton twins, by the method of maximum likelihood using Mx (Neale *et al.* 1999), yielding estimates of genetic and environmental variances, and an overall χ^2 test of goodness-of-fit.

A series of models was also fitted to the data on lifetime use and heavy use, including both models that allowed for separate estimates of genetic, shared environmental and non-shared environmental influences for women and men, and models that assumed that genetic and environmental influences were equal across gender.

Test of equal environments assumption

Finally, similar models to those described above were fitted to data in which the sample was divided into those experiencing similar environments and those experiencing dissimilar environments. A test of the equality of parameter estimates across these two groups provides a test of the equality of environments between monozygotic and dizygotic twin pairs.

RESULTS

Prevalence of cannabis use and dependence

Overall, 60·2% of the sample reported lifetime cannabis use with significantly more males (68·8%) than females (53·2%) reporting lifetime use ($\chi^2 = 150{\cdot}6$, df = 1, $P < 0{\cdot}001$). Approximately 18% of those who reported cannabis use (11·0% of the entire sample) met modified criteria for lifetime cannabis dependence. There were also more men (15·1%) than women (7·8%) meeting criteria for this disorder ($\chi^2 = 81{\cdot}9$, df = 1, $P < 0{\cdot}001$). Additionally, there were significant gender differences in the probability of developing dependence conditional on use: 21·9% of males who had used cannabis developed dependence compared with 14·7% of females ($\chi^2 = 32{\cdot}3$, df = 1, $P < 0{\cdot}001$).

There were no significant age differences in the prevalence of either cannabis use or dependence, as might be expected given that this sample was beyond the average age for initiation of cannabis use (19 in both genders), and was of restricted age range, making age effects due to secular change unlikely. For all but unlike-sex twins, rates of cannabis dependence did not vary significantly between twins from complete pairs and single twins whose co-twin did not participate in the study ($\chi^2 = 3{\cdot}84$, df = 5, $P > 0{\cdot}50$). In the DZUS group rates were significantly elevated in female twins whose male co-twin did not participate ($\chi^2 = 4{\cdot}88$, df = 1, $P < 0{\cdot}05$), implying that cannabis dependent male twins from this group were under sampled.

Twin pair concordances

Table 1 summarizes, for each zygosity group, lifetime prevalence and probandwise concordance rates for cannabis dependence and associated 95% confidence intervals. In females the prevalence of cannabis dependence was similar for monozygotic and dizygotic twins ($\chi^2 = 1{\cdot}82$, df = 2, $P > 0{\cdot}30$) and there was no evidence for higher MZ than DZ same sex twin pair concordance ($\chi^2 = 0{\cdot}43$, df = 1, $P > 0{\cdot}50$).

Table 1. *Lifetime prevalence, twin pair probandwise concordance rates and tetrachoric correlations for cannabis dependence*

Twin group	Sample size			Prevalence		Probandwise concordance		Tetrachoric correlations	
	Complete pairs		Single twins	%	95% CI	%	95% CI	ρ	95% CI
MZ females (MZF)	699		100	7·9	6·5–9·6	35·2	24·1–46·9	0·59	0·42–0·73
DZ same-sex female (DZF)	507		116	8·0	6·4–9·9	28·9	16·2–42·8	0·51	0·29–0·69
MZ male (MZM)	487		154	13·4	11·2–15·8	50·4	40·0–60·5	0·70	0·56–0·80
DZ same-sex male (DZM)	387		158	15·4	12·9–17·9	31·1	21·1–42·1	0·35	0·15–0·53
DZ unlike-sex (DZUS)	655	M:	64	17·5	14·9–20·4	45·2	30·2–60·3	0·44	0·25–0·60
		F:	161	7·5	5·8–9·4	16·8	9·9–23·7		

In males, the prevalence of cannabis dependence was significantly lower in MZ pairs than in the same sex and opposite sex DZ pairs ($\chi^2 = 3{\cdot}82$, df = 1, $P = 0{\cdot}05$). Unlike the evidence for females, probandwise concordance rates were significantly higher in monozygotic (50·4%) compared to same-sex dizygotic (31·1%) twin pairs ($\chi^2 = 9{\cdot}79$, df = 1, $P < 0{\cdot}001$), which is consistent with the hypothesis that there is a genetic contribution to risk of cannabis dependence in males.

Table 1 also shows consistent gender differences in probandwise concordance rates. Specifically, these rates were higher among males from both MZ and same-sex DZ twin pairs. Additionally, the concordance rate among males whose female co-twin was cannabis dependent (45·2%) was higher than the corresponding rate among females whose male co-twin was cannabis dependent (28·9%). It is likely that this elevated rate of concordance for males is a function of the gender difference in the prevalence of cannabis dependence.

Finally, Table 1 shows estimates of twin pair tetrachoric (liability) correlations and their 95% confidence intervals. The twin pair correlation for MZ male twins (0·70) was considerably higher than the corresponding correlation for male DZ twin pairs (0·35), implying a high degree of genetic influence on risk of cannabis use among males. In contrast, the tetrachoric correlation for MZ female twins (0·59) was only slightly higher than that for female DZ twins (0·51), suggesting that genetic factors may be relatively less influential on risk of cannabis dependence among females. However, it can not simply be the case that sibling concordance is determined by genetic factors in men but by shared environmental factors in women, since this would imply a zero tetrachoric correlation in unlike-sex pairs. In fact, the unlike sex pair correlation was substantial (0·44).

Family, social and childhood correlates of cannabis dependence

Table 2 shows the associations between cannabis dependence, psychiatric and other risk factors (parental separation, parental conflict, sexual abuse and measures of conduct disorder, major depression and social anxiety) and co-twin's history of cannabis dependence from multiple logistic regression models. These associations

Table 2. *Associations between cannabis dependence and co-twin's cannabis dependence history controlling for sociodemographic variables, history of sexual abuse and psychiatric disorders*

	Females		Males	
	Odds ratio	95% CI	Odds ratio	95% CI
University education	—	—	0·74	0·55–0·99
Parental divorce	1·62	1·17–2·24	—	—
High parental conflict	—	—	1·59	1·11–2·26
Childhood sexual abuse	1·73	1·24–2·41	—	—
Childhood conduct disorder	4·25	3·03–5·96	3·49	2·72–4·49
Social anxiety	1·50	1·10–2·04	1·36	1·07–1·74
Major depression	1·39	1·01–1·89	1·68	1·29–2·19
MZ co-twin cannabis dependent	6·19	3·23–12·23	4·50	2·70–7·52
DZ female co-twin cannabis dependent	4·54	1·90–11·02	4·09	1·93–8·64
DZ male co-twin cannabis dependent	2·48	1·39–4·85	2·08	1·15–3·78
MZ co-twin unaffected	0·96[NS]	0·66–1·44	0·52	0·36–0·73
DZ female co-twin unaffected	1	—	1	—
DZ male co-twin unaffected	0·71[NS]	0·42–1·22	0·79[NS]	0·56–1·11

NS, Not significant.

are shown separately for women and men. Childhood conduct disorder was a strong predictor of cannabis dependence for both males and females as were a history of major depression and history of social anxiety. Exposure to childhood sexual abuse and parental separation were associated with increased rates of cannabis dependence in women but not men while, conversely, exposure to parental conflict was associated with increased rates of cannabis dependence in men but not in women. Finally, among men having attended university was associated with lowered rates of cannabis dependence.

After control for sociodemographic characteristics, family and psychiatric variables, there remained a significant, and substantial, association between MZ co-twin's cannabis dependence and risk of cannabis dependence: both women (OR = 6·19, 95% CI = 3·23–12·23) and men (OR = 4·50, 95% CI = 2·70–7·52) whose MZ twin was cannabis dependent had elevated odds of meeting criteria for cannabis dependence. Risks of dependence were significantly reduced among men, but not women, whose MZ co-twin was not cannabis dependent. Finally, for both women and men, having a DZ twin who was cannabis dependent was associated with significantly increased risks for developing cannabis dependence. Comparison of odds ratios indicated that, among men, the increased risk of cannabis dependence was significantly higher among individuals with a MZ affected than a DZ affected twin ($\chi^2 = 4{\cdot}5$, df = 1, $P < 0{\cdot}05$). In contrast, in women the odds ratios for those with MZ and DZ affected co-twins were not significantly different ($\chi^2 = 0{\cdot}4$, df = 1, $P > 0{\cdot}40$).

In summary, the pattern of results displayed in Table 2 is consistent with the hypothesis that, even after sociodemographic factors, family environment, exposure to abuse and measures of psychiatric disorder have been taken into account, there is a significant residual genetic influence on risk of cannabis dependence in men, and a significant residual shared environmental influence on risk in women.

The heritability of cannabis dependence in women and men

Under a model allowing for genetic, shared environmental and non-shared environmental factors, and assuming no gender differences in the magnitude of these effects, estimates of the total variance in liability to cannabis dependence attributable to each of these sources were 44·7% (95% CI = 15·0–72·2), 20·1% (95% CI = 0–43·6) and 35·3% (95% CI = 26·4–45·7) respectively. This model gave an excellent fit to the observed data ($\chi^2 = 9{\cdot}36$, df = 11, $P > 0{\cdot}50$).

There was no evidence of significant gender differences in genetic and environmental parameters ($\chi^2 = 1{\cdot}75$, df = 2, $P > 0{\cdot}20$). However, we also could not reject the hypothesis that twin pair resemblance for cannabis dependence was determined by genetic and shared environmental effects in men, but by shared environmental effects only in women (see Table 3 for parameter

Table 3. *Proportions of variance (and 95% confidence intervals) in cannabis use, heavy use and dependence explained by genetic, shared environment and non-shared environmental influences*

	% Variance explained by			Model fit[1]		
	Genetic	Shared environment	Non-shared environment	χ^2	df	*P*
Dependence						
(*a*) Model assuming no sex differences[2]						
	44·7 (15·0–72·2)	20·1 (0·0–43·6)	35·3 (26·4–45·7)	9·36	11	> 0·50
(*b*) Model assuming sex-dependent genetic effect[2,3]						
Men	44·6 (16·7–66·3)	22·9 (16·7–44·4)	32·5 (21·5–46·3)	9·12	10	> 0·50
Women	0	56·4 (43·7–67·4)	43·6 (32·5–56·2)			
(*c*) Model (*b*) but estimating genetic as well as shared environmental parameters for women						
Men	55·9% (23·3–77·0)	12·9% (0·0–39·6)	31·2% (20·5–44·9)	7·61	9	> 0·50
Women	21·4% (0·0–67·1%)	38·8% (0·0–65·1%)	39·9% (27·0–54·4%)			
Lifetime use[4]						
Men	66·8 (9·1–75·1)	0·0 (0·0–49·7)	33·1 (24·8–43·2)	7·20	9	> 0·60
Women	45·4 (18·0–69·9)	25·5 (3·1–49·0)	29·1 (22·7–37·0)			
Heavy use[5]	64·3 (42·4–83·6)	13·6 (0·0–32·3)	21·8 (16·0–29·0)	8·26	11	> 0·60

[1] Model fit based on LR chi-squared goodness-of-fit test.
[2] Model estimates separate thresholds for: (*i*) MZ males; (*ii*) DZ males; (*iii*) singleton females from unlike-sex pairs; and (*iv*) all other females, based on tests for prevalence differences.
[3] As these models were fitted to contingency table data, liability variances have been standardized to unity. Hence, there are only two free parameters in model *a* and three free parameters in model *b*.
[4] Model estimates separate thresholds for: (*i*) female twins from complete DZ unlike-sex pairs; (*ii*) MZ male singleton twins; (*iii*) all other female twins; (*iv*) all other male twins. Prevalence of cannabis use was significantly elevated in female twins from unlike-sex pairs compared to other groups ($\chi^2 = 5{\cdot}82$, df = 1, $P = 0{\cdot}016$) but did not differ significantly between the remaining female twin groups ($\chi^2 = 1{\cdot}57$, df = 4, $P = 0{\cdot}81$). Likewise, prevalence of cannabis use was significantly lower in single twins from male MZ pairs ($\chi^2 = 6{\cdot}83$, df = 1, $P = 0{\cdot}009$) but did not differ for the remaining male twin groups ($\chi^2 = 4{\cdot}32$, df = 4, $P = 0{\cdot}36$).
[5] Model estimates separate thresholds for: (*i*) male twins from DZ unlike sex pairs; (*ii*) single male twins from unlike sex-pairs; (*iii*) remaining male twins; (*iv*) all female twins. Prevalence of heavy use was significantly higher in males from unlike sex pairs ($\chi^2 = 4{\cdot}72$, df = 1, $P = 0{\cdot}030$) and from single males from unlike sex pairs ($\chi^2 = 4{\cdot}93$, df = 1, $P = 0{\cdot}026$). However, rates of heavy cannabis use did not differ between remaining male twin groups ($\chi^2 = 2{\cdot}15$, df = 3, $P = 0{\cdot}54$) or between any of the female twin groups ($\chi^2 = 4{\cdot}06$, df = 5, $P = 0{\cdot}54$).

estimates). This model, while less parsimonious than the model with no sex-dependent genetic and environmental parameters (it has one fewer degree of freedom) also gave a good fit to the observed data ($\chi^2 = 9{\cdot}12$, df = 10, $P > 0{\cdot}50$). Thus, while we can safely conclude that there are significant genetic effects on risk of cannabis dependence in men, we cannot state for certain whether or not there are genetic effects on cannabis dependence risk in women, and whether or not there are shared environmental effects on cannabis dependence risk overall.

Test of equal environments assumption

To test the equal environments assumption a set of subsidiary analyses were conducted in which the sample were divided into high similarity and low similarity environment on the basis of their self-reported childhood environments. The models described above were then fitted to this data to examine whether estimates of tetrachoric correlations for cannabis dependence varied between twins reporting similar environments and those reporting dissimilar environments. The results of these analyses revealed no significant differences ($\chi^2 = 2{\cdot}42$, df = 5, $P = 0{\cdot}79$) indicating that, for the environmental measures available for analysis, the assumption of equal environments between monozygotic and dizygotic twin pairs was not violated for this sample.

The heritability of lifetime cannabis use and heavy use

Also shown in Table 3 are estimates of the proportion of variance in lifetime cannabis use and heavy use that could be explained by genetic factors, shared environment and non-shared environmental factors. For heavy use, a model estimating separate parameters for women and men did not provide a significant improvement of model fit over a model assuming equality of parameter estimates across gender ($\chi^2 = 1{\cdot}04$, df = 2, $P > 0{\cdot}90$). In contrast, for lifetime use, a model estimating separate parameters for males and females provided an improved fit over a model assuming no gender differences ($\chi^2 = 5{\cdot}03$, df = 2, $P < 0{\cdot}10$).

The parameter estimates from these models are summarized in Table 3. There was evidence of substantial heritability for both heavy use (64·3% of the variance) and lifetime use (45·4% of the variance in women and 66·8% of the variance in men). For lifetime use, there was evidence of significant shared environmental influences among women (25·5%) while there was no evidence of shared environment influences on lifetime cannabis use among men.

DISCUSSION

In our analyses of a large national Australian sample of young adult female and male twins we observed high rates of both cannabis use and dependence. Exposure to cannabis use appeared normative since 60% of the sample reported having used cannabis on at least one occasion. There were slight gender differences in the lifetime prevalence of cannabis use with more men (68·8%) than women (53·2%) reporting having used the drug. While many of those reporting cannabis use had used it only infrequently, 11·0% of the sample (15·1% of men and 7·8% of women) met our modified criteria for cannabis dependence.

The genetics of cannabis dependence

The results of model fitting indicated a substantial degree of heritability of cannabis dependence, with our estimate suggesting that 44·7% of the variance in risk for cannabis dependence could be attributed to genetic factors. This estimate is similar to, but lower than, previous estimates derived from US twin studies: 62% in female twins (Kendler & Prescott, 1998) and 58% in male twins (Kendler *et al*. 2000*a*). Both these estimates fall within the 95% confidence intervals computed in the present study. The convergence of estimates based on samples of different ages, from different societies and using different definitions of cannabis dependence, supports the conclusion that a substantial component of the liabiltity to develop cannabis related problems is mediated by genetic factors. Similarly, our finding that the equal environments assumption was not violated for these analyses supports the conclusion that some component of the variance in cannabis dependence arises from genetic influences.

We did not find significant gender differences in the heritability of cannabis dependence. However, a model assuming both genetic and shared environmental factors influence risk of cannabis dependence in men and that there are shared environmental but not genetic influences on risk of cannabis dependence in women provided an equally good fit to the data. The finding of a non-significant gender difference in genetic influences on cannabis dependence does not necessarily contradict the finding of there being no significant genetic effects on cannabis dependence in women. Rather, it may be a reflection of reduced statistical power for studying genetic effects in women, given their lower base rate of cannabis dependence. Nonetheless, it is not possible, on the basis of this analysis, to rule out the possibility that there are no genetic effects on risk of cannabis dependence among women.

This finding parallels the results reported by van den Bree *et al*. (1998) who suggested that genetic factors may be relatively more influential in the aetiology of drug use problems in males than in females but is in sharp contrast to the results reported by Kendler & Prescott (1998) who analysed data from a sample of female-only twins and concluded that genetic factors explain 62% of the variance in liability for cannabis dependence. Nonetheless, the 95% confidence interval for our estimate of the genetic contribution to cannabis dependence liability in women was very broad (0–67·1%). It is clear that there is a need for more research into potential gender differences in both the magnitude of genetic effects on cannabis dependence and the origins of any such gender differences.

While a model assuming equal genetic influences in males and females may seem counterintuitive, given the consistently higher rate of cannabis dependence among males reported in most epidemiological studies, equality of genetic influences does not imply equal prevalence. Rather, this model supports the conclusion, paralleled in the alcohol literature (Heath *et al*. 1997), that women with the same degree of genetic or shared environmental risk as men are less likely to become cannabis dependent. Thus, while 31% of men with a cannabis dependent male DZ twin developed cannabis dependence, only 17% of women with a cannabis dependent male twin developed dependence. Conversely, the risks of developing cannabis dependence

among those with a DZ co-twin who was cannabis dependent appeared greater if that twin was female (28·9% for women and 45·2% for men). Again, this pattern of results implies that women who become cannabis dependent are likely on average to have a greater degree of genetic or shared environmental risk than men who become affected.

Risk factors for cannabis dependence

Our findings indicated that being less well educated, having been exposed to family conflict or divorce, having experienced sexual abuse and reporting a history of conduct disorder, major depression and social anxiety were all associated with significantly increased risks of cannabis dependence. These factors are in broad agreement with the range of factors previously identified as being associated with increased risks of substance use and substance related problems (see review by Hawkins *et al*. 1992).

Specifically, there is much research linking social disadvantage and family dysfunction with increased risks for substance related problems (Hawkins *et al*. 1992; Miller, 1997) while the findings of both longitudinal (Fergusson *et al*. 1996) and genetically informative research (Dinwiddie *et al*. 2000; Kendler *et al*. 2000*b*; Nelson *et al*. 2002) implicate exposure to sexual abuse as having a causal role in the aetiology of substance use disorders and related problems. Additionally, the present study documented associations between cannabis dependence and a range of psychiatric disorders including childhood conduct disorder, major depression and social anxiety. There is an accumulation of literature identifying childhood conduct disorder as a precursor to the development of substance related problems (Robins & Price, 1991; Fergusson & Lynskey, 1998). By comparison, there is less published research exploring the associations between cannabis use and other psychiatric conditions such as depression or anxiety disorders. The observed associations between cannabis dependence (and other substance related problems) and measures of mental health may reflect: (*a*) a causal association in which poor mental health leads to increased risks of cannabis use; (*b*) a causal association in which cannabis use leads to deteriorating mental health or; (*c*) is non-causal and, instead reflects the effects of other related risk factors that act to increase risks of both poor mental health and substance related problems. Our strategy of controlling for life-time disorder when testing for a residual association between respondent's and co-twin's cannabis dependence is a conservative one, since it may cause us to underestimate the association with co-twin history if cannabis dependence is, in fact, affecting other outcomes.

The results of this study suggest that psychiatric disorders and other risk factors play only a modest role in the aetiology of cannabis dependence. Controlling for such risk factors, the cannabis dependence history reported by the respondent's co-twin remained a strong and significant predictor of respondent cannabis dependence status.

Environmental and genetic influences on lifetime cannabis use and heavy use

Results of model fitting indicated substantial genetic influences on both of these outcomes while shared environmental influences appeared only negligible. Our findings, while broadly replicating those of previous reports showing strong genetic influences on measures of cannabis use (Kendler & Prescott, 1998; van den Bree *et al*. 1998; Maes *et al*. 1999; Kendler *et al*. 2000*a*), also suggest some intriguing differences with prior research. In particular, previous studies have typically reported stronger genetic influences on cannabis dependence than on cannabis use. For example, both Kendler & Prescott (1998) and Kendler *et al*. (2000*a*) reported higher estimates of genetic influences for cannabis dependence (62% and 58% of the variance respectively) than for cannabis use (40% and 33% of the variance) while both van den Bree (1998) and Maes *et al*. (1999) highlighted the relative importance of shared environmental factors in the aetiology of cannabis use rather than dependence.

In contrast, the current study has reported that genetic factors are relatively more important in the aetiology of cannabis use than of dependence. The reasons for these apparent discrepancies are unclear but may be due, at least in part, to cultural and age related differences between the samples studied. Nonetheless, it is important to note that the estimates of genetic and environmental influences on each of the cannabis use measures assessed in the current study fall within the confidence intervals

of estimates from previous studies. Furthermore, all studies are consistent in reporting that genetic factors play an important role in the aetiology of cannabis use and cannabis related problems, assessed using a variety of definitions, and that shared environmental factors are relatively less influential.

Summary and implications

The results of this and previous studies of cannabis and other drug dependence indicate that a substantial component of the liability to experiencing drug-related problems arises from genetic factors. This finding parallels those from the tobacco (Kendler *et al*. 1999; True *et al*. 1999) and alcohol literatures (Heath, 1995; Heath *et al*. 1997; Schuckit, 1999; True *et al*. 1999) that a substantial component of the liability to heavy, problematical or dependent use of these substances can be attributed to genetic factors. However, in comparison to the more extensively researched areas of tobacco and alcohol use, considerably less is known about the routes by which genetic influences on cannabis and other drug dependence arise. From the analyses presented here it is clear that sociodemographic, family and psychiatric risk-factors play only a modest role in mediating genetic and environmental influences on cannabis dependence.

Within the tobacco and alcohol literature a number of factors have been identified, including personality factors that may mediate genetic influences on initiation (Heath *et al*. 1995), differences in alcohol sensitivity (Heath *et al*. 1999) or physiological responses to drug use, which may mediate escalation in, and persistence of use (Heath & Madden, 1995). Clearly, there is a need of further research into the mechanisms underlying genetic susceptibilities to cannabis as well as other drug-related problems. While less intensively researched than the factors underlying liability to tobacco and alcohol dependence, it is probable that the factors and processes mediating genetic influences on cannabis dependence will parallel those underlying tobacco and alcohol dependence.

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