

Duration of cannabis use — a novel phenotype?

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Abstract

Although cannabis is the most commonly used illicit drug, duration of cannabis use is typically short, with many of those who initiate cannabis use ceasing use by their late twenties. In this paper we analyze data from a volunteer Australian cohort of 6265 male and female twins to examine whether the duration of cannabis use is an informative phenotype for future genetic analyses. Genetic modeling indicated: (a) moderate genetic influences on duration of cannabis use in both males (41%; 95% CI=31–51) and females (55%; 95% CI=46–63); (b) strong genetic influences on cannabis dependence in both males (72%, 95% CI=61–81) and females (62%, 95% CI=48–74); (c) no evidence of shared environmental influences on duration of cannabis use or on cannabis dependence in either males or females. Importantly, this model fitting indicated that a substantial component of genetic influences ($r_g = .90$, 95% CI = .77–.99 (males); .70, 95% CI = .57–.83 (females)) on duration of cannabis use was shared with those influencing liability to cannabis dependence. While there were high genetic correlations in both women and men, lifetime duration of cannabis may be uniquely informative in assessing components of liability to cannabis use.

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1. Introduction

Cannabis is the most commonly used illicit drug in the U.S. with current estimates suggesting that 45.7% of 12th graders have ever used cannabis (Johnston, O'Malley, Bachman, & Schulenberg, 2005),

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40.2% of the household population aged 12 years or older report lifetime cannabis use (SAMHSA, 2005) and 1.5% meet the criteria for past year cannabis abuse or dependence (Compton, Grant, Colliver, Glantz, & Stinson, 2004). While some lifetime experience with cannabis is common, relative to the use of tobacco and alcohol, an individual's cannabis use career is typically considerably shorter with many people who start using cannabis in their mid teens stopping use by their mid to late twenties. For example, Chen and Kandel (1995) reported that approximately 75% of cannabis users have ceased using the drug by age 34–35, compared with only 8% of lifetime alcohol users who have ceased alcohol use by that age. Observations that the typical period of cannabis use is substantially shorter than that for tobacco or alcohol have led to recognition that, at the population level, the potential for harm caused by chronic long term use is substantially lower for cannabis than it is for tobacco or alcohol (Robins, 1995).

Relative to the accumulated research literature on the etiology and health effects of tobacco and alcohol use, there is also considerably less research examining cannabis use (Hall, Degenhardt, & Lynskey, 2001). Nonetheless, there is consistent evidence of moderate to high heritabilities for cannabis use, abuse and dependence: estimates of the heritability of cannabis use have ranged from 17% to 72% (Kendler & Prescott, 1998; Kendler, Karkowski, Neale, & Prescott, 2000; Kendler et al., 2002; Lynskey et al., 2002; Maes et al., 1999; McGue, Elkins, & Iacono, 2000; Miles et al., 2001; Rhee et al., 2003; van den Bree, Johnson, Neale, & Pickens, 1998), those for abuse have ranged from 34% to 76% (Kendler & Prescott, 1998; Kendler et al., 2000; Tsuang et al., 1998) and those for dependence have ranged from 34% to 78% (Kendler & Prescott, 1998; Kendler et al., 2000; Lynskey et al., 2002; Rhee et al., 2003; van den Bree et al., 1998; for a review see Agrawal & Lynskey, *in press*).

Given previous research indicating that a diverse range of cannabis related phenotypes are influenced by genetic factors but that there is wide variation in the duration of cannabis use (with many individuals using cannabis for relatively brief periods of time), it is of interest to consider whether duration of cannabis use is itself influenced by heritable factors. Specifically, while duration of use is likely to be highly correlated with risk of dependence, it is not necessarily the case that all long duration users of cannabis will develop dependence and, conversely, some relatively short duration cannabis users may develop dependence. Such a pattern of associations would suggest that there are some factors (genetic or environmental) influencing duration of use/propensity to use that are separate from those influencing the development of cannabis dependence.

Additionally, the research literature has identified potential sex differences in the development of cannabis use and dependence. While numerous studies report that males have a higher prevalence across a range of cannabis related phenotypes including lifetime use, frequency of use and cannabis abuse or dependence (e.g., Compton et al., 2004; Johnston et al., 2005; SAMHSA, 2005), several studies report that female cannabis users are at greater risk for the development of cannabis dependence relative to males who report a similar level of cannabis use (Kandel, Chen, Warner, Kessler, & Grant, 1997; Ridenour et al., 2005). Thus, males may be at a heightened risk for cannabis dependence because more males use cannabis while, conversely, the risk of dependence among users may be higher in females. There is also inconsistent evidence that there may be sex differences in the heritability of cannabis dependence with several studies reporting greater heritability of cannabis related phenotypes, including use and dependence, among males than among females (Lynskey et al., 2002; van den Bree et al., 1998).

Thus, the current paper has two central aims:

- (a) To describe variations in lifetime duration of cannabis use within a general population sample of twins and to estimate the extent to which such variations are influenced by additive genetic, shared

environmental and non-shared environmental influences. Additionally, by utilizing a sample of both male and female twins (including unlike-sex twin pairs) we are able to examine the extent to which the magnitude of genetic and environmental influences varies by sex.

- (b) To document the associations between lifetime duration of cannabis use and risk of cannabis dependence and to estimate the extent of overlap or correlation between the risk factors (both genetic and environmental) associated with duration of cannabis use and those associated with liability to cannabis dependence. These analyses provide a critical test of the utility of putatively novel phenotypes such as duration of use, by estimating the extent to which they are influenced by similar or different factors from those that influence established and commonly used phenotypes such as dependence.

2. Method

2.1. Sample

Interviewees were members of the young adult cohort of the Australian Twin Register, a volunteer twin panel who were born between 1964 and 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 (Heath et al., 2001). The data presented in this report are derived from responses to a telephone interview conducted by lay interviewers during the period 1996–2000 (Heath et al., 2001; Knopik et al., 2004; Nelson et al., 2002). Verbal 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.

The initial panel recruited in 1980–82 comprised 4262 twin pairs. Of these, 5.9% of pairs could not be located in 1996–2000, even after extensive efforts. Diagnostic interviews were conducted during 1996–2000 with 6265 individuals (including 2706 complete pairs: 688 MZF, 503 DZF, 484 MZM, 388 DZM, 643 DZO), 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 median age at assessment of respondents was 30 (range=24–36).

2.2. Assessments

A structured diagnostic interview designed for genetic studies on alcoholism, the SSAGA (Buchholz 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 illicit drug use, abuse and an abbreviated assessment of illicit drug dependence, lifetime history of alcohol dependence, major depression and childhood conduct disorder as well as a non-diagnostic assessment of history of social anxiety (Heath et al., 1997; Statham et al., 1998). There was also an assessment of nicotine dependence adapted from the Composite International Diagnostic Interview (CIDI; Cottler, Robins, & Helzer, 1989; Robins et al., 1988). 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 knowledge of the history of the twin or his or her co-twin or family members.

2.3. Measures

2.3.1. Duration of cannabis use

Respondents were asked whether they had ever used cannabis: 68.8% of males and 53.2% of females reported lifetime cannabis use. Those reporting lifetime cannabis use were then asked the age at which they first used cannabis and how old they were when they last used cannabis. A measure of the duration of cannabis use (assessed in years) was then constructed by subtracting the age of first use from the age of most recent use. This was then categorized to form a five level variable, with approximately equal numbers of subjects in each category. The five levels represented: (a) individuals whose cannabis use had spanned less than one year; (b) those who reported using cannabis for between 1 and 3 years; (c) individuals who reported using cannabis for between 4 and 7 years; (d) individuals who reported using cannabis for between 8 and 11 years and (e) those who reported using cannabis for 12 years or longer.

2.3.2. Lifetime 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. Assessment of dependence was based on the following four criteria: using the drug more frequently or for longer periods than intended; needing larger amounts to achieve an effect (tolerance); continued use of the drug despite use causing emotional problems; recurrent desire to cut down on use. Individuals who reported two or more of these symptoms for a specific drug class were considered to be dependent on that drug. While this measure did not provide formal DSM-IV diagnostic criteria, previous analyses exploring the validity of these modified criteria indicated that they had both excellent sensitivity (96.7%) and specificity (94.6%) when compared with full DSM-IV cannabis dependence criteria (Lynskey et al., 2002).

2.3.3. Zygosity

Zygosity was assessed using standard questions for zygosity assignment (Nichols & Bilbro, 1966), a method which has been shown to yield 95% accuracy when compared with genotyping (Kasriel & Eaves, 1976).

2.4. Statistical analyses

The associations between sex and lifetime cannabis use were assessed using the odds ratio and its associated 95% confidence interval, with these estimates adjusted for the non-independence of observations from twin pairs using the Huber–White variance estimator, as implemented in Stata (Stata Corporation, 2005). Similarly, we assessed the association between the duration of cannabis use and rates of lifetime cannabis dependence by Wald chi-square, again adjusted for the non-independence of observations from members of a twin pair using the Huber–White variance estimator as implemented in Stata.

Quantitative genetic theory has been described in detail previously (Plomin, 1990). In brief, the correlation for identical twin pairs (MZs) will be greater than the correlation for fraternal twin pairs (DZs) if a behavior is genetically influenced (because MZs share 100% of their genes and DZs share an average of 50% of their segregating genes). If the MZ correlation is greater than the DZ correlation, but not twice the DZ correlation, there is also evidence of some shared environmental influences (environmental influences that make family members similar to each other; shared to the same extent for MZ and DZ twins by definition). If the MZ correlation is more than twice the DZ correlation, there is evidence of non-additive genetic influence for the behavior (because non-additive genetic influences require that the members of the twin pair receive the same allele from both parents, which only happens 25% of the time on average for DZ twin pairs, and again happens 100% of the time for MZ pairs). The extent to which the MZ twin correlation is less than 1.0 indicates the magnitude of non-shared environmental influences (i.e., those environmental influences that make members of a twin pair different from each other). When data are collected from unlike-sex twin pairs, it becomes possible to test for sex-specific genetic and environmental influences by comparing the similarity of same-sex DZ pairs to the similarity of unlike-sex DZ pairs. Although the correlation coefficients for the zygosity groups give an indication of the underlying genetic and environmental contributions to a given behavior, they cannot be used to assess the significance of specific influences; it is necessary to use structural equation models to determine the significance of genetic and shared environmental influences.

In the present analyses, standard genetic model fitting procedures (Eaves, Last, Young, & Martin, 1978; Kendler, Heath, Martin, & Eaves, 1986; Neale, Boker, Xie, & Maes, 1999) were used in a bivariate Cholesky model (described in detail by Neale & Cardon, 1992), to allow for both the estimation of additive genetic, shared environmental and non-shared environmental influences on the duration of cannabis use and the estimation of the extent to which these sources of variation in duration of use were correlated with the corresponding sources of variation in cannabis dependence. In these models we controlled for potential influences of (current) age by creating 3 dummy variables for age, dividing respondents into four roughly equal-sized age groups (24–27 year-olds=the comparison group=20%; 28–29=25%; 30–31=31%; 32–36=24%). All three dummy variables were used in all analyses. The regression was assumed to be linear across all threshold levels (i.e., the impact of being in a given age group was the same for the transition from duration 0 to 1, from 1 to 2, from 2 to 3, and from 3 to 4; there were four thresholds for duration and there was one threshold for dependence). These models were fitted to the data using the method of maximum likelihood estimation as implemented in the statistical package Mx (Neale et al., 1999).

3. Results

3.1. *Duration of cannabis use and lifetime cannabis dependence*

Some lifetime experience with cannabis was common in this cohort with 68.8% of males and 53.2% of females reporting using cannabis on at least one occasion (OR=1.94, 95% CI=1.73–2.18). There was, however, a wide variation in the self-reported duration of cannabis use with approximately one in five lifetime cannabis users reporting duration of cannabis use of less than one year. Table 1 shows the duration of cannabis use, classified into five groups, for both males and females: there were significant

Table 1

Duration of cannabis use (years) and rates of cannabis dependence by sex among sample members reporting lifetime cannabis use

	Males		Females	
	Duration of use (%)	Dependence (%)	Duration of use (%)	Dependence (%)
Less than 1 year	16.7	0.6	26.3	0.0
1–3 years	17.0	4.9	19.2	7.7
4–7 years	19.8	16.9	19.8	13.6
8–11 years	23.0	29.5	19.0	21.7
12+ years	23.5	46.2	15.8	41.1
<i>N</i>	1907		1822	

sex differences in the duration of cannabis use with higher percentages of male lifetime users reporting relatively long durations of use ($\chi^2_{1df}=66.2, p<.001$).

Table 1 also shows strong associations between duration of cannabis use and risk of cannabis dependence; individuals who reported using cannabis for less than one year had near-zero risks of cannabis dependence while 46.2% of males and 41.1% of females who had used cannabis for more than 12 years met criteria for cannabis dependence. Logistic regression modeling showed a strong association between duration of cannabis use and risk of cannabis dependence (OR=2.47, 95% CI=2.20–2.78) but no significant associations between sex and risk of cannabis dependence (OR=1.14, 95% CI=.58–2.25) or between the interaction between sex and duration of use (OR=1.03, 95% CI=.87–1.21) and risk of cannabis dependence. This indicates that the risk of cannabis dependence conditional on a given duration of cannabis use was consistent for males and females.

3.2. Intra-individual and within-pair tetrachoric correlations between duration of cannabis use and cannabis dependence

Duration of cannabis use and cannabis dependence were highly correlated with the estimated correlation between these phenotypes being .61. Although not shown in Table 2 intra-individual correlation between duration and dependence did not vary significantly across zygosity (as would be expected): There were also substantial within trait cross-twin correlations for both duration of cannabis use and for dependence (see Table 2). Interestingly, for duration of use, these correlations were

Table 2

Within- and across trait, across-twin correlations for duration of cannabis use and cannabis dependence

	Within trait; across twin		Across trait, across twin
	Duration	Dependence	
Overall	.32	.51	.35
MZF	.54	.59	.35
MZM	.44	.70	.44
DZF	.25	.50	.34
DZM	.24	.35	.34
DZO	.07	.31	.24

NB: Within-twin correlations between duration and dependence did not vary by zygosity and, overall, these phenotypes were correlated .61.

approximately twice as strong in monozygotic as in dizygotic twin pairs, a pattern that is strongly suggestive of additive genetic influences on duration of cannabis use. Similarly, within-pair correlations were substantially higher for MZ males than for DZ females, but only marginally high in MZ females than in DZ females, suggesting stronger evidence for heritability of cannabis dependence in males than in females. Finally, across trait across-twin pair correlations were also substantial suggesting the influence of shared familial influences (both genetic and environmental) on these phenotypes.

3.3. Bivariate genetic modeling of duration of cannabis use and lifetime cannabis dependence

From an initial model that contained additive genetic (A), shared environmental (C), and non-shared environmental (E) influences with proportions of variance attributable to each effect equated across sex, submodels were tested to find the most parsimonious solution (see Table 3). Because the initial analyses indicated that there were no shared environmental influences specific to duration of use (i.e., the path was estimated at its lower bound of .001), this parameter was not included in the base model. Model fit improved significantly when we allowed for the proportion of variance attributable to A differ for men and women ($\Delta\chi^2=8.856$ with 3df, $p<.05$), but did not when we allowed the proportion of variance attributable to C to vary across sex ($\Delta\chi^2=3.321$ with 3df, $p>.05$). Further analyses indicated that C could be removed from the model without a significant decrement in fit ($\Delta\chi^2=.658$ with 2df, $p>.05$). These analyses also indicated that the genetic correlation (r_g) between duration and dependence was significantly higher for males than for females ($\Delta\chi^2=4.635$ with 1df, $p<.05$). Thus, the final model was one in which both duration of use and dependence were influenced by two sources of variation (additive genetic and non-shared environmental), with the proportions of variance attributable to A and E and r_g and r_e allowed to vary across sex.

The results of this model are summarized in Table 4 and indicate:

- (a) Additive genetic factors made moderate contributions to liability to duration of cannabis use, with these influences stronger in females (55%) than in males (41%). Similarly, there were substantial genetic contributions to liability to cannabis dependence, with these influences stronger in males (72%) than females (62%).
- (b) Shared environmental factors did not contribute to variations in liability for either measure.
- (c) Importantly, these models also provided estimates of the extent to which the genetic and environmental factors associated with duration of use and those associated with cannabis

Table 3

Bivariate genetic model fitting for duration of cannabis use and cannabis dependence^a

Model ^b	Comparison model	$\Delta\chi^2$	Δdf	p
1 A, C, and E equated for men and women, no C specific to dependence	–			
2 Allow gender differences in C	1	3.321	3	.34
3 Allow gender differences in A	1	8.856	3	.03
4 Drop C*	3	4.658	2	.10
5 Equate r_g for men and women	1	4.635	1	.03

^aAll models control for age. ^bIndent indicates that the model is a submodel of the one above. r_g indicates genetic correlation.

*Final model.

Table 4

Bivariate genetic models for duration of cannabis use and cannabis dependence: proportions of variance (CI)^a

Sex	Variance comp. ¹	Duration of cannabis use	Cannabis dependence	Correlation
Males	a ²	0.41 (0.31–0.51)	0.72 (0.61–0.81)	0.90 (0.77–0.99)
	e ²	0.59 (0.49–0.69)	0.28 (0.19–0.39)	0.26 (0.08–0.44)
Females	a ²	0.55 (0.46–0.63)	0.62 (0.48–0.74)	0.70 (0.57–0.83)
	e ²	0.45 (0.37–0.54)	0.38 (0.26–0.53)	0.40 (0.23–0.57)

¹a²= additive genetic, e²= non-shared environmental.^aAll models control for age.

dependence were correlated. There was a substantial genetic correlation (r_g) between duration of cannabis use and lifetime cannabis dependence in both women (0.70) and men (0.90). The non-shared environmental correlation (r_e) was modest but still significant for both men and women (0.26 and 0.40 respectively). Thus, the models suggested that 49–81% of genetic effects and 7–16% of non-shared environmental influences on the two measures were overlapping. Importantly, in no case did the upper bound of the confidence intervals reach 1.00, indicating that although there is an overlap, there is also variance (both genetic and environmental) that is specific to the duration of cannabis use versus the development of cannabis dependence.

4. Discussion

While lifetime use of cannabis was common in this sample of twins, there was also wide variation in the duration of cannabis use with approximately one in five cannabis users reporting that they had used cannabis for less than one year while a similar percentage reported that their use of cannabis had spanned over 12 years or longer. Consistent with previous epidemiological evidence on sex differences in cannabis use, abuse and dependence (Compton et al., 2004; Johnston et al., 2005; SAMHSA, 2005), males were more likely than females to report prolonged duration of cannabis use. While these were mirrored by sex differences in risk of cannabis dependence, there was no significant interaction between sex and duration of cannabis use on risk of cannabis dependence, indicating that the probability of dependence conditional on a given duration of cannabis use did not vary for males and females.

Again consistent with an expanding literature documenting substantial heritability of cannabis related phenotypes (see review by Agrawal and Lynskey, in press), results of genetic model fitting indicated a substantial genetic component to duration of cannabis use, with genetic factors being more influential on duration of cannabis use in females (.55) than in males (.41). Conversely, for cannabis dependence there was evidence to suggest that genetic factors were more influential in males (0.72) than in females (0.62).

There were strong associations between duration of cannabis use and lifetime risks of cannabis dependence; nearly half of those who had used cannabis for twelve or more years met criteria for cannabis dependence compared with less than 1% of those who had used it for less than one year. Genetic model fitting indicated that much of this association likely arose from genetic influences that acted to increase risks of both longer use of cannabis and of cannabis dependence. Importantly, these models suggested that although there is considerable genetic overlap in these factors, there are probably

some genetic factors influencing duration of cannabis use that are independent from those influencing cannabis dependence.

Given our reliance on a twin sample, we have analyzed heritability solely as a latent factor, yet it is interesting to speculate on the nature of genetic influences on cannabis duration/dependence and the ways in which genetic influences on these phenotypes may differ. In considering this, it is important to re-emphasize that there are likely multiple sources of genetic variation in liability to complex phenotypes such as cannabis duration or dependence (Agrawal & Lynskey, *in press*). These may include factors related to personality domains such as novelty seeking (Agrawal et al., 2004) that may increase liability to experimentation and factors affecting drug metabolism (Tyndale, 2003). It is possible to speculate that, in so far as there is an incomplete overlap in the genetic factors associated with duration of cannabis use and those associated with cannabis dependence, genetic influences on cannabis dependence may include relatively more factors relating to drug metabolism while those related relatively more strongly to duration of use may be more strongly associated with factors such as antisocial behavior. Such considerations have potential implications for the design of gene-discovery efforts: for example, sampling strategies that target dependence conditional on a relatively low duration of use may have heightened power for detecting genes associated with drug metabolism.

It is also important to consider a number of potential limitations to our analysis. Firstly, although our measure of cannabis dependence has been shown to have both high specificity and high sensitivity (Lynskey et al., 2002), it was incomplete (see Section 2.3). Further research is needed to determine whether the genetic correlation with duration of use may be higher for some components of dependence than for others. Secondly, there was some age variation in our sample and it was not the case that all sample members would have completed their cannabis use career nor passed through the period of maximum “risk” for cannabis cessation. We have attempted to address this issue by including current age as a control variable in our analyses, with such control having only minimal impact on parameter estimates. Although surprising, the limited influence of control for current age on model parameters is likely due to the truncated age range of the sample, with all sample members having been born during the period 1964–1971. Finally, in this study we have relied on retrospective reports of the age at first cannabis use (a critical component of our measure of duration of cannabis use). Despite potential limitations of retrospective recall, previous studies have generally concluded that self-reported ages of onset for substance use are generally reliable (Cottler et al. 1989; Grant, Harford, Dawson, Chou, & Pickering, 1995; Johnson & Mott, 2001; Parra, O’Neill, & Sher, 2003).

Despite these limitations, our current findings confirm that there is a considerable variation in the duration of lifetime cannabis use, that variations in duration of cannabis use are moderately heritable, strongly associated with lifetime risks of cannabis dependence and that there is considerable – but incomplete – overlap between the genetic factors associated with duration of cannabis use and those associated with risk of lifetime cannabis dependence. Our analyses demonstrate one strategy whereby the potential utility of novel phenotypes for use in genetic studies can be evaluated using family based and other genetically informative research designs. Finally, they also highlight the developmental nature of cannabis (and other substance) use disorders and the potential for the development and exploration of novel phenotypes based on transitions in substance use. For example, it seems possible that the speed of transitions (e.g., from first use to the development of first dependence symptom; Chen et al, 2005) may also provide important clues to the genetic architecture of risk for the development of these disorders.

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References

- Agrawal, A., Jacobson, K. C., Prescott, C. A., & Kendler, K. S. (2004). A twin study of personality and illicit drug use and abuse/dependence. *Twin Research*, 7, 72–81.
- Agrawal A., Lynskey M. T. (in press). The genetic epidemiology of cannabis use, abuse and dependence: A review. *Addiction*.
- American Psychiatric Association (1994). *Diagnostic and statistical manual of mental disorders — 4th edition (DSM-IV)*. Washington, D.C.: American Psychiatric Association.
- Bucholz, K. K., Cloninger, C. R., Dinwiddie, S. H., Hesselbrock, V. M., Nurnberger, J. I., & Reich, T., et al. (1994). A new, semi-structured psychiatric interview for use in genetic linkage studies: A report of the reliability of the SSAGA. *Journal of Studies on Alcohol*, 55, 149–158.
- Chen, C. -Y., O'Brien, M. S., & Anthony, J. C. (2005). Who becomes cannabis dependent soon after onset of use? Epidemiological evidence from the United States, 2000–2001. *Drug and Alcohol Dependence*, 79, 11–22.
- Chen, K., & Kandel, D. B. (1995). The natural history of drug use from adolescence to the mid-thirties in a general population sample. *American Journal of Public Health*, 85, 41–47.
- Cottler, L. B., Robins, L. N., & Helzer, J. E. (1989). The reliability of the CIDI-SAM: A comprehensive substance abuse interview. *British Journal of Addiction*, 84, 801–814.
- Compton, W. M., Grant, B. F., Colliver, J. D., Glantz, M. D., & Stinson, F. S. (2004). Prevalence of marijuana use disorders in the United States 1991–1992 and 2001–2002. *Journal of the American Medical Association*, 291, 2114–2121.
- Eaves, L. J., Last, K., Young, P. A., & Martin, N. G. (1978). Model-fitting approaches to the analysis of human behavior. *Heredity*, 41, 249–320.
- Grant, B. F., Harford, T. C., Dawson, D. A., Chou, P. S., & Pickering, R. P. (1995). The alcohol use disorder and associated disabilities interview schedule (AUDADIS): Reliability of alcohol and drug modules in a general population sample. *Drug and Alcohol Dependence*, 39, 37–44.
- Hall, W., Degenhardt, L., & Lynskey, M. (2001). *The health and psychological effects of cannabis use*. Canberra, ACT: Commonwealth Department of Health and Aging.
- Heath, A. C., Bucholz, K. K., Madden, P. A., Dinwiddie, S. H., Slutske, W. S., & Bierut, L. J., et al. (1997). Genetic and environmental contributions to alcohol dependence risk in a national twin sample: consistency of findings in women and men. *Psychological Medicine*, 27, 1381–1396.
- Heath, A. C., Howells, W., Kirk, K. M., Madden, P. A., Bucholz, K. K., & Nelson, E. C., et al. (2001). Predictors of non-response to a questionnaire survey of a volunteer twin panel: Findings from the Australian 1989 twin cohort. *Twin Research*, 4, 73–80.
- Johnson, T. P., & Mott, J. A. (2001). The reliability of self-reported age of onset of tobacco, alcohol and illicit drug use. *Addiction*, 96, 1187–1198.
- Johnston, L. D., O'Malley, P. M., Bachman, J. G., & Schulenberg, J. E. (2005). Monitoring the future national survey results on drug use, 1975–2004. *Volume I: Secondary school students (NIH Publication No. 05-5727)*. Bethesda, MD: National Institute on Drug Abuse.
- Kandel, D., Chen, K., Warner, L. A., Kessler, R. C., & Grant, B. (1997). Prevalence and demographic correlates of symptoms of last year dependence on alcohol, nicotine, marijuana and cocaine in the U.S. population. *Drug and Alcohol Dependence*, 44, 11–29.
- Kasriel, J., & Eaves, L. J. (1976). The zygosity of twins: Further evidence on the agreement between diagnosis by blood groups and written questionnaires. *Journal of Biosocial Science*, 8, 263–266.
- Kendler, K. S., Heath, A. C., Martin, N. G., & Eaves, L. J. (1986). Symptoms of anxiety and depression in a volunteer twin population: The etiologic role of genetic and environmental factors. *Archives of General Psychiatry*, 43, 213–221.

- Kendler, K. S., Karkowski, L. M., Neale, M. C., & Prescott, C. A. (2000). Illicit psychoactive substance use, heavy use, abuse and dependence in a US population-based sample of male twins. *Archives of General Psychiatry*, 57, 261–269.
- Kendler, K. S., Neale, M. C., Thornton, L. M., Aggen, S. H., Gilman, S. E., & Kessler, R. C. (2002). Cannabis use in the last year in a US national sample of twin and sibling pairs. *Psychological Medicine*, 32, 551–554.
- Kendler, K. S., & Prescott, C. A. (1998). Cannabis use, abuse and dependence in a population-based sample of female twins. *American Journal of Psychiatry*, 155, 1016–1022.
- Knopik, V. S., Heath, A. C., Madden, P. A., Bucholz, K. K., Slutske, W. S., & Nelson, E. C., et al. (2004). Genetic effects on alcohol dependence risk: Re-evaluating the importance of psychiatric and other heritable risk factors. *Psychological Medicine*, 34, 1519–1530.
- Lynskey, M. T., Heath, A. C., Nelson, E. C., Bucholz, K. K., Madden, P. A. F., & Slutske, W. S., et al. (2002). Genetic and environmental contributions to cannabis dependence in a national young adult twin sample. *Psychological Medicine*, 32, 195–207.
- McGue, M., Elkins, I., & Iacono, W. G. (2000). Genetic and environmental influences on adolescent substance use and abuse. *American Journal of Medical Genetics*, 96, 671–677.
- Maes, H. H., Woodard, C. E., Murrelle, L., Meyer, J. M., Silberg, J. L., & Hewitt, J. K., et al. (1999). Tobacco, alcohol and drug use in eight-to sixteen-year-old twins: The Virginia twin study of adolescent behavioral development. *Journal of Studies on Alcohol*, 60, 293–305.
- Miles, D. R., van den Bree, M. B. M., Gupman, A. E., Newlin, D. B., Glantz, M. D., & Pickens, R. W. (2001). A twin study on sensation seeking, risk taking behavior and marijuana use. *Drug and Alcohol Dependence*, vol. 62 (pp. 57–68).
- Neale, M. C., Boker, S. M., Xie, G., & Maes, H. H. (1999). *MX: Statistical modeling* (5th edition). Richmond, VA: Department of Psychiatry, Medical College of Virginia.
- Neale, M. C., & Cardon, L. R. (1992). *Methodology for genetic studies of twins and families*. Dordrecht: Kluwer Academic Publishers.
- Nelson, E. C., Heath, A. C., Madden, P. A. F., Cooper, M. L., Dinwiddie, S. H., & Bucholz, K. K., et al. (2002). The consequences and correlates of childhood sexual abuse — a retrospective examination using the twin study design. *Archives of General Psychiatry*, 59, 139–145.
- Nichols, R. C., & Bilbro, W. C. (1966). The diagnosis of twin zygosity. *Acta Genetica et Statistica Medica*, 16, 265–275.
- Parra, G. R., O'Neill, S. E., & Sher, K. J. (2003). Reliability of self-reported age of substance involvement onset. *Psychology of Addictive Behaviors*, 17, 211–218.
- Plomin, R. (1990). *Nature and nurture: An introduction to human behavioral genetics*. Pacific Grove, CA: Brooks/Cole.
- Rhee, S. H., Hewitt, J. K., Young, S. E., Corley, R. P., Crowley, T. J., & Stallings, M. C. (2003). Genetic and environmental influences on substance initiation, use, and problem use in adolescents. *Archives of General Psychiatry*, 60, 1256–1264.
- Ridenour, T. A., Maldonado-Molina, M., Compton, W. M., Spitznagel, E. L., & Cottler, L. B. (2005). Factors associated with the transition from abuse to dependence among substance abusers: Implications for a measure of addictive liability. *Drug and Alcohol Dependence*, 80, 1–14.
- Robins, L. N. (1995). The natural history of substance use as a guide to setting policy. *American Journal of Public Health*, 85, 12–13.
- Robins, L. N., Wing, J., Wittchen, H. U., Helzer, J. E., Babor, T. F., & Burke, J., et al. (1988). The Composite International Diagnostic Interview. An epidemiologic instrument suitable for use in conjunction with different diagnostic systems and in different cultures. *Archives of General Psychiatry*, 45, 1069–1077.
- Stata Corporation (2005). *Stata statistical software: Release 9*. College Station, TX: Stata Corporation.
- Satham, D. J., Heath, A. C., Madden, P. A., Bucholz, K. K., Bierut, L., & Dinwiddie, S. H., et al. (1998). Suicidal behavior: An epidemiological and genetic study. *Psychological Medicine*, 28, 839–855.
- Substance Abuse and Mental Health Services Administration (SAMHSA) (2005). *Overview of findings from the 2004 National Household Survey on Drug Abuse*. Rockville, MD: Office of Applied Statistics.
- Tsuang, M. T., Lyons, M. J., Meyer, J. M., Doyle, T., Eisen, S. A., & Goldberg, J., et al. (1998). Co-occurrence of abuse of different drugs in men: The role of drug specific and shared vulnerabilities. *Archives of General Psychiatry*, 55, 967–972.
- Tyndale, R. F. (2003). Genetics of alcohol and tobacco use in humans. *Annals of Medicine*, 35, 94–121.
- van den Bree, M. B., Johnson, E. O., Neale, M. C., & Pickens, R. W. (1998). Genetic and environmental influences on drug use and abuse/dependence in male and female twins. *Drug and Alcohol Dependence*, 52, 231–241.