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# The familial aggregation of cannabis use disorders

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## Abstract

**Aims—**The aim of this paper is to examine the familial aggregation of cannabis use disorders and other psychiatric conditions among first-degree relatives and spouses of probands with a cannabis use disorder.

**Design—**Controlled family study methods.

**Setting—**Out-patient psychiatric clinics and the local community (same geographic area).

**Participants—**Two hundred and sixty-two probands with a life-time history of cannabis use disorder, alcohol dependence, anxiety disorders or no history of any disorder, and their first-degree relatives and spouses.

**Measurements—**Cannabis use disorders and other DSM-III-R disorders in the relatives and spouses using the Schedule for Affective Disorders and Schizophrenia.

**Findings—**Results reveal an elevated risk of life-time history of cannabis use disorders among siblings [odds ratio (OR: 3.6), adult offspring (OR): 6.9], and spouses (OR: 4.4) of probands with cannabis use disorders. There is a latent familial factor underlying cannabis use disorders that was shared partially with alcohol abuse/dependence. Comorbid mood and anxiety disorders aggregated independently from cannabis use disorders in families. Equal elevation in the magnitude of the association among the first-degree adult relatives and spouses of probands with a cannabis use disorder suggests the probable contribution of both environmental and genetic factors.

**Conclusions—**These findings support a family-based approach to drug abuse intervention and the importance of future research concerning environmental mediators of familial transmission of drug abuse.

### Keywords

Anxiety disorder; assortative mating; cannabis; comorbidity; family study; gene-environment interaction; mood disorder; substance use disorder

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**Declarations of interest**
None.

## INTRODUCTION

Cannabis is the most widely available illicit psychoactive drug in the United States [1]. Nearly 40% of 12th graders in the United States reported marijuana use during the past year [2] and 6% of the general population over age 12 used marijuana or hashish over the previous month [3]. The life-time prevalence rate of cannabis abuse or dependence has been estimated recently at 8.5%, and both conditions are associated strongly with other psychiatric disorders [4,5]. The risk factors for cannabis use, abuse and dependence are similar to other substances, and include characteristics such as age of exposure, early reaction to cannabis, economic factors, substance availability, religious involvement, delinquent behaviors, peer relationships and attitudes towards the future [5–12]. The risk factors for use differ in some respects from those that may lead to heavy use, abuse or dependence [11,13–18], but the cumulative number of risk factors an individual possesses is a significant predictor of substance-related problems [10–12,14, 17,19].

Controlled family studies [20], involving the identification of individuals with and without a particular disorder followed by blinded assessment of disorder rates in their relatives, have confirmed many of the findings from clinical or epidemiological investigations as well as demonstrated the extent to which substance use disorders are familial [16,21–26]. While some specificity of familial aggregation is found for particular drugs [8,27–29], parental substance abuse is associated with a wide range of behavior problems and drug use among exposed children. Other pathways of familial aggregation include sibling substance abuse [27,29] as well as assortative mating, where a high degree of concordance is observed for substance use disorders between spouses [23,30–42]. Concerning the underlying causes of familial aggregation, twin studies have shown that genetic factors explain a portion of the variance in sibling concordance for cannabis abuse/dependence [43–48]. Adoption studies have confirmed the heritability of these conditions, but also the importance of interactions between genetic and environmental factors in the development of a substance use disorders [16,28,43–46,49–51]. With few exceptions [43], genetic factors have been found to play a more potent role in the etiology of severe patterns of drug use, particularly abuse or dependence, than early stages of use, which appear to be determined more strongly by environmental influences [28,44,46].

In a previous controlled family study of several predominant drugs of abuse, we found an eightfold increased risk of drug use disorders among relatives of affected probands compared to those of psychiatric and unaffected controls [8]. The current study was designed to examine more specifically the patterns of cannabis use disorders in the first-degree relatives and spouses of probands with a life-time history of cannabis use disorder compared to relatives of probands with alcohol dependence, anxiety disorders and controls without these disorders. We address the following questions: (i) what is the magnitude of familial aggregation of cannabis use disorders in relatives of probands with these disorders, compared to relatives of probands with alcohol dependence, anxiety disorders or no disorder; (ii) is there concordance between spouses for cannabis use disorders; and (iii) are there shared familial factors underlying cannabis use disorders, alcohol dependence and other mental disorders?

## METHODS

### Sample characteristics

**Probands—**Probands in the present analyses are a subset of participants in a large family study examining comorbidity of substance use disorders and anxiety disorders [52]. In order to investigate the specificity of familial aggregation of cannabis use disorders, the present analyses are restricted to 36 probands with predominant cannabis use disorder, 89 probands with alcohol dependence (47 with and 42 without anxiety disorders), 76 probands with anxiety disorder only, 61 controls without a life-time history of disorder and 215 first-degree relatives

and spouses of the different proband groups. Probands with opioid or cocaine dependence, recruited as part of the larger study, were excluded from the present analyses. All probands were white, because we have examined familial aggregation of substance abuse in Hispanics and African Americans in separate studies. Table 1 reports the socio-demographic characteristics of the proband groups studied. The probands were 40 years old on average, with an equal sex distribution.

Probands were recruited through several out-patient clinics for substance and anxiety disorders, and through community random digit dialing in the greater New Haven, Connecticut area. After providing a complete description of the study to the subjects, written informed consent was obtained. Probands were assigned to lifetime diagnostic groups based on an algorithm designed to reflect predominant level of psychopathology: DSM-III-R diagnoses of cannabis use disorder, alcohol dependence and an anxiety disorder; alcohol dependence without an anxiety disorder; anxiety disorders only (social phobia or panic disorder with or without agoraphobia); and normal controls with no life-time history of a DSM-III-R Axis I disorder. Based upon review by clinicians with expertise in substance abuse, probands were excluded from the study if there was evidence of significant organic mental impairment, schizoaffective disorder or schizophrenia. The normal controls were recruited using a random digit dialing procedure in which they were drawn from the same general population as those of the affected probands. The control group was subjected to the same protocol as the treatment groups.

**Relatives—**Inclusion criteria required that permission be obtained first from probands to contact living relatives, of whom 123 (57%) were interviewed directly, either in person or by telephone. The interview rates did not differ significantly between proband diagnostic groups, and all analyses controlled for the effect of interview status. Interviewed family members included all first-degree adult relatives (parents, children, siblings), as well as past and/or current spouses (individuals married to the proband or cohabitating for at least 6 years).

## Overview of procedures

**Diagnostic interview—**Adult psychiatric disorders were established using the semi-structured Schedule for Affective Disorders and Schizophrenia (SADS), current and life-time versions [53], which was modified to include more detailed information on substance use including patterns and interrelationships of drug use. The SADS differs from other diagnostic instruments in that it uses a semi-structured format and is administered by experienced clinical interviewers, as opposed to the highly structured formats of the Composite International Diagnostic Interview (CIDI) or Diagnostic Interview Schedule (DIS) used by lay interviewers. Interviewers with experience in clinical psychiatry and/or substance abuse conducted the diagnostic interviews to establish diagnoses using DSM-III-R criteria. Reliability was established at the study initiation and was tested periodically throughout the study. Kappas derived from joint ratings of individual interviews were generally higher for substance abuse/dependence (0.72–0.94) than for anxiety or affective disorders (0.54–0.78) across the first three series of training sessions. Comparison of diagnoses obtained through direct face-to-face interview versus telephone interview showed high levels of agreement across all diagnostic categories [54].

**Family history information—**Family history information was obtained using a modified version of the Family History–Research Diagnostic Criteria [55] to obtain DSM-III-R diagnoses in adults and children. The modified version is more similar to instruments such as the Family Interview for Genetic Studies and enabled the collection of more extensive information on patterns and sequelae of drug and alcohol use as well as the extent of the informant's knowledge on the index subject.

**Diagnostic procedures—**Diagnoses of mental and substance use disorders were based upon all available information, including the diagnostic interview, family history reports and medical records, using the best estimate method of diagnoses. Each drug of abuse was characterized by: age at onset, quantity, frequency, chronicity, substance of choice, number of symptoms and severity. Best-estimate diagnoses were made by clinicians with extensive experience in the evaluation and treatment of substance abuse, and who were made blind with respect to the diagnostic status of the probands when making best estimates of the relatives. Interview status was included as a covariate in the analyses because of the well-established underestimation of diagnoses in non-interviewed relatives. Direct interviews and family history are far more concordant for observable disorders such as drug abuse and behavior disorders than for less readily observable disorders such as mood and anxiety disorders.

### Statistical analysis

Logistic regression analyses were used to estimate odds ratios (OR) and 95% confidence intervals (CI) for the differences in the proportion of affected versus unaffected first-degree relatives and spouses, controlling for proband sex, interview status (direct versus telephone interview), sample source (i.e. clinic versus community), relative sex and relative age. The association between DSM-III-R cannabis use disorders and the number of affected parents was assessed using the Armitage test for trend in proportions [56]. The association between the age-at-onset of cannabis use disorders between pairs of relatives was assessed using the statistic developed by Clayton & Oakes [57,58]. The Clayton–Oakes concordance measures the broad 'correlation' of two ages of onset through the so-called cross-ratio. The cross-ratio can be viewed as the OR of the two events occurring within a short time-interval under the assumption that this ratio is time-constant. In addition, we assessed the family aggregation, covariate effects and potential interaction between familial contribution and covariates using a frailty regression model [59,60]. In essence, a latent variable is introduced for each family of the study and is used to summarize the familial association. Conditional on this latent variable, cannabis use disorders are assumed to follow an ordinary logistic regression model. Thus, the marginal distribution of cannabis use disorders is described by a mixture logistic regression model. The presence and significance of the latent variable in the mixture logistic regression model is indicative of familial aggregation. The main advantage of this regression model is its flexibility to adjust for covariate effects or to examine the interactions between covariates and an underlying familial effect. We refer to Zhang & Merikangas [60] for a detailed description of the model.

## RESULTS

Table 2 presents the concordance of frequency tables of cannabis abuse or dependence between probands and their first-degree relatives and spouses and adjusted ORs. The siblings of the probands who had cannabis abuse or dependence had a greater risk (OR 3.6, 95% CI: 2.0–6.5) of cannabis abuse or dependence than those of probands without a cannabis use disorder. Similarly, adult offspring of probands with a cannabis use disorder had a greater risk of developing a cannabis use disorder (OR 6.9, 95% CI: 1.4–33.5) compared to those relatives of probands without a cannabis use disorder. Probands with a cannabis use disorder were more than four times (OR 4.4, 95% CI: 1.9–10.1) more likely to have spouses with a cannabis use disorder than those without a history of a cannabis use disorder. The associations between the ages-at-onset of probands and siblings, and probands and spouses were of similar magnitude (4.07 for siblings and 4.12 for spouses), both of which were highly significant (*P*-values less than 0.0001).

Table 3 presents the results of the multivariate regression analysis using the frailty model that assesses the risks of cannabis use disorder among probands and relatives (latent familial factor).

The ORs and 95% CIs from the multivariate model are reported for the effects of proband cannabis use disorder, sex and comorbid disorders on cannabis use disorders in relatives adjusting for the effects of age, sex, comorbid disorders and interview status of relatives. Effects and significance are reported for each of those risk factors.

There was a strong association between alcohol dependence, antisocial personality and cannabis use disorders in relatives, whereas there was no significant association between anxiety disorders or major depression and cannabis use disorders. Similarly, comorbid anxiety, depression and antisocial personality disorder in probands with a cannabis use disorder were not associated with cannabis use disorders in relatives. In contrast, the association between alcohol dependence in the probands and a cannabis use disorder in the relatives demonstrates that there may be common underlying risk factors for these two disorders. Finally, neither the sex of the proband nor the sex of the relative nor their interaction modified the familial association between substance use disorders in probands and relatives.

## DISCUSSION

The primary aim of this study was to investigate the familial aggregation of cannabis use disorders among spouses and first-degree relatives of affected probands. The results show a significant degree of familial aggregation of cannabis use disorders among both siblings and adult offspring of probands with a cannabis use disorder. The increased rate of these disorders among siblings of affected probands supports previous research by Bierut *et al.* [27] and others [54,61], who showed high levels of specificity of familial transmission of cannabis use disorders within sibling pairs relative to controls, even after restricting the data to include only those pairs who have tried these illicit drugs. Similar to previous high-risk studies of substance abuse in the children of parents with substance use disorders [7,9,21,23,31,32,62], we found a significant elevation in life-time rates of cannabis abuse/dependence among adult offspring. This familial concordance may result from several factors including behavior modeling, shared environment, accessibility and genetic factors.

We also found a high concordance rate for cannabis use disorders between probands and their spouses: 47% of the male spouses and 25% of the female spouses of probands with a cannabis use disorder also had a cannabis use disorder. From an examination of patterns of spouse concordance before and after marriage to the probands, it could be observed that the age of onset of cannabis occurred prior to the marriage in 89% of the couples concordant for cannabis use disorders. While this may suggest that primary or secondary (social homogamy) assortative mating is implicated in spousal concordance, the average age of onset for cannabis use and the average age of marriage render it plausible that cohabitation may also influence cannabis use and potentially lead to more regular use, abuse and dependence. Moreover, the nearly identical concordance rates among siblings, who are biological relatives (OR 4.5), and spouses who are not biologically related (OR 4.4), highlights the probability that both environmental and genetic influences are implicated in the familial transmission of cannabis use disorders. That is, while the choice of a spouse who is concordant for cannabis may be understood as an environmental factor, it may increase both environmental determinants (e.g. modeling, availability of cannabis) as well as genetic similarities between spouses that in turn increase aggregation of cannabis use disorders within families. Irrespective of the mechanisms for spouse concordance, our findings suggest that future studies of the genetic transmission of drug use disorders incorporate assortative mating as it may distort segregation ratios and affect the distribution of affected and unaffected families in the population.

Our finding that familial concordance for cannabis abuse/dependence persisted after controlling for comorbid disorders in probands suggests that affective and other behavior disorders aggregate independently from these disorders. Similar conclusions were drawn from

previous uncontrolled family studies [21,25,63], indicating that anxiety, affective and antisocial personality disorder could either be pre-morbid risk factors or consequences of cannabis use disorders. In contrast, our finding of cross-concordance between cannabis use disorders and alcohol dependence in probands and relatives suggests that shared familial factors underlie both these forms of substance dependence. This finding confirms previous observations from family and twin studies of alcohol-dependent probands [48,64–66], but extends the findings to cross-generational transmission. The lack of cross-generational transmission of cannabis abuse or dependence with other disorders such as anxiety suggests that their association at an individual level may be best explained by behavioral or psychological mechanisms [67].

To our knowledge, this is the first controlled family study that tests the inter-generational transmission of cannabis use disorders, independent of other substances. This information supplements the current knowledge derived largely from twin studies as well as from previous uncontrolled family studies of substance abuse and controlled family studies of cannabis use disorders in alcoholic probands. There are several unique design aspects of this study that enhance its contribution to the knowledge of cannabis use disorder etiology, including: selection of probands recruited from both community and treatment settings; direct interviews with relatives blind to probands' disorders to ensure more accurate classification; inclusion of probands with alcohol dependence without a cannabis use disorder as a substance-disordered comparison group to enable evaluation of specificity; inclusion of a control group in which similar diagnostic and assessment methods were used; and incorporation of psychiatric comorbidity among probands and relatives in the design and analyses.

Concerning limitations of this study, the focus on cannabis abuse and dependence diagnoses may overlook a substantial percentage of individuals who experience cannabis-related problems and who are at risk for meeting diagnostic criteria for abuse or dependence in the future [68–70]. An additional consideration is that different generations may be more or less likely to use cannabis depending on changing societal views on this substance. In this regard, the prevalence of 12-month cannabis use in the United States has remained stable between 1990 and 2000 [71], with a modest increase in the prevalence of cannabis use disorders over this period (due possibly to increasing potency of the substance). Considerable variation has, none the less, been seen over time concerning the legal penalties for cannabis use since its placement under the jurisdiction of the Department of Justice following the Controlled Substances Act of 1970. These societal contexts, as well as changes in cannabis availability, may explain partially differences in rates observed between age cohorts, in particular for the parents of probands. Other limitations include the restriction of the sample to white residents of Connecticut, the lack of direct interviews for all relatives and statistical power concerns in light of a potentially large number of latent variables coupled with relatively small sample size. A final important consideration is the generalization of findings in light of the 'two worlds' of clinical and general population samples [72]. Although the sampling strategy recruited probands intentionally from both treatment and community settings to reduce biases that may affect familial aggregation [73], the comparability of these sample sources remains a subject of debate.

In conclusion, these findings add to the body of research that provides evidence not only for common familial factors underlying substance abuse in general, but also highlights the need to examine risk factors that may be specific to particular substances. Future research is crucial for elucidating the roles of genetic and environmental factors in the transmission of cannabis use disorders and their apparent familial association with alcoholism, as well as for identifying sources of heterogeneity in the etiology of cannabis abuse, particularly with respect to the role of comorbid psychiatric disorders and polysubstance abuse. Finally, the high spouse concordance for cannabis use disorders suggests that offspring of these probands are a

particularly elevated risk for the development of these conditions themselves and should be targeted in future prevention and intervention studies.

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## References

1. Compton WM, Conway KP, Stinson FS, Colliver JD, Grant BF. Prevalence, correlates, and comorbidity of DSM-IV anti-social personality syndromes and alcohol and specific drug use disorders in the United States: results from the National Epidemiological Survey on alcohol and related conditions. J Clin Psychiatry 2005;66:677–85. [PubMed: 15960559]
2. Johnston, LD.; O'Malley, P.; Bachman, JG.; Schulenberg, JE. Monitoring the Future, National Results on Adolescent Drug Use: Overview of Key Findings, 2003. Bethesda, MD: National Institute of Drug Abuse; 2004. NIH Publication no. 04-5506
3. National Household Survey on Drug Abuse. Substance Abuse and Mental Health Services Administration: Summary of Findings from the 2003 National Household Survey on Drug Abuse. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2004.
4. Stinson FS, Ruan WJ, Pickering R, Grant BF. Cannabis use disorders in the USA: prevalence, correlates and comorbidity. Psychol Med 2006;36:1447–60. [PubMed: 16854249]
5. Wittchen H-U, Frohlich C, Behrendt S, Gunther A, Rehm J, Zimmermann P, et al. Cannabis use and cannabis use disorders and their relationship to mental disorders: a 10-year prospective-longitudinal community study in adolescents. Drug Alcohol Depend 2007;88:S60–70. [PubMed: 17257779]
6. Bovasso GB. Cannabis abuse as a risk factor for depressive symptoms. Am J Psychiatry 2001;158:2033–7. [PubMed: 11729021]
7. Martin CS, Earleywine M, Blackson TC, Vanyukov MM, Moss HB, Tarter RE. Aggressivity, inattention, hyperactivity, and impulsivity in boys at high and low risk for substance abuse. J Abnorm Child Psychol 1994;22:177–203. [PubMed: 8064028]
8. Merikangas KR, Stolar M, Stevens DE, Goulet J, Preisig MA, Fenton B, et al. Familial transmission of substance use disorders. Arch Gen Psychiatry 1998;55:973–9. [PubMed: 9819065]
9. Moss HB, Majumder PP, Vanyukov M. Familial resemblance for psychoactive substance use disorders: behavioral profile of high risk boys. Addict Behav 1994;19:199–208. [PubMed: 8036966]
10. Van Den Bree M, Pickworth WB. Risk factors predicting changes in marijuana involvement in teenagers. Arch Gen Psychiatry 2005;62:311–9. [PubMed: 15753244]
11. Von Sydow K, Lieb R, Pfister H, Hofler M, Wittchen H-U. What predicts incident use of cannabis and progression to abuse and dependence? A 4-year prospective examination of risk factors in a community sample of adolescents and young adults. Drug Alcohol Depend 2002;68:49–64. [PubMed: 12167552]
12. Windle M, Wiesner M. Trajectories of marijuana use from adolescence to young adulthood: predictors and outcomes. Dev Psychopathol 2004;16:1007–27. [PubMed: 15704825]
13. Brook JS, Brook DW, Gordon AS, Whiteman M, Cohen P. The psychosocial etiology of adolescent drug use: a family interactional approach. Genet Soc Gen Psychol Monogr 1990;116:111–267. [PubMed: 2376323]
14. Brook JS, Kessler RC, Cohen P. The onset of marijuana use from preadolescence and early adolescence to young adulthood. Dev Psychopathol 1999;11:901–14. [PubMed: 10624731]
15. Brook JS, Newcomb MD. Childhood aggression and unconventionality: impact on later academic achievement, drug use, and workforce involvement. J Genet Psychol 1995;156:393–410. [PubMed: 8543928]
16. Cadoret RJ, Troughton E, O'Gorman T, Heywood E. An adoption study of genetic and environmental factors in drug abuse. Arch Gen Psychiatry 1986;43:1131–6. [PubMed: 3778110]

17. Glantz, MD.; Weinberg, NZ.; Miner, LL.; Colliver, JD. The etiology of drug abuse: mapping the paths. In: Glantz, MD.; Hartel, CR., editors. Drug Abuse: Origins and Interventions. Washington, DC: American Psychological Association; 1999. p. 3-45.

18. Kandel DB, Yamaguchi K, Chen K. Stages of progression in drug involvement from adolescence to adulthood: further evidence for the gateway theory. J Stud Alcohol 1992;53:447–57. [PubMed: 1405637]

19. Chen CY, O'Brien MS, Anthony JC. Who becomes cannabis dependent soon after onset of use? Epidemiological evidence from the United States: 2000–2001. Drug Alcohol Depend 2005;79:11–22. [PubMed: 15943940]

20. Weissman MM, Merikangas KR, John K, Wickramaratne P, Prusoff BA, Kidd KK. Family-genetic studies of psychiatric disorders. Developing technologies. Arch Gen Psychiatry 1986;43:1104–16. [PubMed: 3532996]

21. Croughan, J. The Contributions of Family Studies to Understanding Drug Abuse, in Studying Drug Abuse. New Brunswick, NJ: Rutgers University Press; 1985.

22. Gfroerer J. Correlation between drug use by teenagers and drug use by older family members. Am J Drug Alcohol Abuse 1987;13:95–108. [PubMed: 3687887]

23. Hopfer CJ, Stallings MC, Hewitt JK, Crowley TJ. Family transmission of marijuana use, abuse, and dependence. J Am Acad Child Adolesc Psychiatry 2003;42:834–41. [PubMed: 12819443]

24. Meller WH, Rinehart R, Cadoret RJ, Troughton E. Specific familial transmission in substance abuse. Int J Addictions 1988;23:1029–39.

25. Mirin SM, Weiss RD, Griffin ML, Michael JL. Psychopathology in drug abusers and their families. Compr Psychiatry 1991;32:36–51. [PubMed: 2001619]

26. Mirin SM, Weiss RD, Michael J, Griffin ML. Psychopathology in substance abusers: diagnosis and treatment. Am J Drug Alcohol Abuse 1988;14:139–57. [PubMed: 3052036]

27. Bierut L, Dinwiddie S, Begleiter H, Crowe R, Hesselbrock V, Nurnberger J, et al. Familial transmission of substance dependence: alcohol, marijuana, cocaine, and habitual smoking: a report from the collaborative study on the genetics of alcoholism. Arch Gen Psychiatry 1998;55:982–8. [PubMed: 9819066]

28. Tsuang MT, Lyons MJ, Eisen SA, Goldberg J, True W, Nong L, et al. Genetic influences on DSM-III-R drug abuse and dependence: a study of 3372 twin pairs. Am J Med Genet 1996;67:473–7. [PubMed: 8886164]

29. Avenevoli S, Merikangas KR. Familial influences on adolescent smoking. Addiction 2003;98:1–20. [PubMed: 12752359]

30. Homish GG, Leonard KE, Cornelius JR. Predictors of marijuana use among married couples: the influence of one's spouse. Drug Alcohol Depend 2007;91:121–8. [PubMed: 17600639]

31. Hopfer CJ, Crowley TJ, Hewitt JK. Review of twin and adoption studies of adolescent substance use. J Am Acad Child Adolesc Psychiatry 2003;42:710–9. [PubMed: 12921479]

32. Merikangas, KR.; Rounsaville, BJ.; Prusoff, BA. Familial factors in vulnerability to substance abuse. In: Glantz, M.; Pickens, R., editors. Vulnerability to Drug Abuse. Washington, DC: American Psychological Association; 1992. p. 75-97.

33. Anglin MD, Booth MW, Kao CF, Harlow LL, Peters K. Similarity of behavior within addict couples. Part II. Addiction-related variables. Int J Addict 1987;22:583–607. [PubMed: 3623746]

34. Galbaud Du Fort G, Bland RC, Newman SC, Boothroyd LJ. Spouse similarity for lifetime psychiatric history in the general population. Psychol Med 1998;28:789–802. [PubMed: 9723136]

35. Hall RL, Hesselbrock VM, Stabenau JR. Familial distribution of alcohol use: I. Assortative mating in the parents of alcoholics. Behav Genet 1983;13:361–72. [PubMed: 6639561]

36. Hall RL, Hesselbrock VM, Stabenau JR. Familial distribution of alcohol use: II. Assortative mating of alcoholic probands. Behav Genet 1983;13:373–82. [PubMed: 6639562]

37. McLeod JD. Spouse concordance for alcohol dependence and heavy drinking: evidence from a community sample. Alcohol Clin Exp Res 1993;17:1146–55. [PubMed: 8116823]

38. Price RA, Chen K-H, Cavalli-Sforza LL, Feldman MW. Models of spouse influence and their application to smoking behavior. Soc Biol 1982:14–29.

39. Rimmer J, Winokur G. The spouses of alcoholics: an example of assortative mating. Dis Nerv Syst 1972;33:509–11. [PubMed: 4648452]
40. Schuckit MA, Tipp JE, Kelner E. Are daughters of alcoholics more likely to marry alcoholics? Am J Drug Alcohol Abuse 1994;20:237–45. [PubMed: 8042605]
41. Windle M. Mate similarity, heavy substance use and family history of problem drinking among young adult women. J Stud Alcohol 1997;58:573–80. [PubMed: 9391916]
42. Winokur G, Reich T, Rimmer J, Pitts FN. Alcoholism. 3. Diagnosis and familial psychiatric illness in 259 alcoholic probands. Arch Gen Psychiatry 1970;23:104–11. [PubMed: 5428294]
43. Agrawal A, Jacobson KC, Prescott CA, Kendler KS. A twin study of personality and illicit drug use and abuse/dependence. Twin Res 2004;7:72–81. [PubMed: 15053856]
44. Kendler KS, Prescott CA. Cannabis use, abuse, and dependence in a population-based sample of female twins. Am J Psychiatry 1998;155:1016–22. [PubMed: 9699687]
45. Lynskey MT, Heath AC, Nelson EC, Bucholz KK, Madden PA, Slutske WS, et al. Genetic and environmental contributions to cannabis dependence in a national young adult twin sample. Psychol Med 2002;32:195–207. [PubMed: 11871371]
46. Rhee SH, Hewitt JK, Young SE, Corley RP, Crowley TJ, Stallings MC. Genetic and environmental influences on substance initiation, use, and problem use in adolescents. Arch Gen Psychiatry 2003;60:1256–64. [PubMed: 14662558]
47. True WR, Xian H, Scherrer JF, Madden PA, Bucholz KK, Heath AC, et al. Common genetic vulnerability for nicotine and alcohol dependence in men. Arch Gen Psychiatry 1999;56:655–61. [PubMed: 10401514]
48. Tsuang MT, Lyons MJ, Meyer JM, Doyle T, Eisen SA, Goldberg J, et al. Co-occurrence of abuse of different drugs in men: the role of drug-specific and shared vulnerabilities. Arch Gen Psychiatry 1998;55:967–72. [PubMed: 9819064]
49. Cadoret, RJ. Genetic and environmental factors in initiation of drug use and the transition to abuse. In: Glantz, M.; Pickens, R., editors. Vulnerability to Drug Abuse. Washington, DC: American Psychological Association; 1992. p. 99-113.
50. Cadoret RJ, Yates WR, Troughton E, Woodworth G, Stewart MA. Adoption study demonstrating two genetic pathways to drug abuse. Arch Gen Psychiatry 1995;52:42–52. [PubMed: 7811161]
51. Cadoret RJ, Yates WR, Troughton E, Woodworth G, Stewart MA. An adoption study of drug abuse/dependency in females. Compr Psychiatry 1996;37:88–94. [PubMed: 8654068]
52. Merikangas KR, Stevens DE, Fenton B, Stolar M, O'Malley S, Woods SW, et al. Co-morbidity and familial aggregation of alcoholism and anxiety disorders. Psychol Med 1998;28:773–88. [PubMed: 9723135]
53. Endicott J, Spitzer RL. A diagnostic interview: the schedule for affective disorders and schizophrenia. Arch Gen Psychiatry 1978;35:837–44. [PubMed: 678037]
54. Conger R, Rutter M, Conger K. The family context of adolescent vulnerability and resilience to alcohol use and abuse. Sociol Stud Child 1994;6:55–86.
55. Andreasen NC, Endicott J, Spitzer RL, Winokur G. The family history method using diagnostic criteria. Reliability and validity. Arch Gen Psychiatry 1977;34:1229–35. [PubMed: 911222]
56. Armitage P. Tests for linear trends in proportions and frequencies. Biometrics 1955;11:375–86.
57. Clayton D. A model for association in bivariate life-tables and its application in epidemiological studies of family tendency in chronic disease incidence. Biometrika 1978;65:141–51.
58. Oakes D. A concordance test for independence in the presence of censoring. Biometrics 1982;38:451–5. [PubMed: 7052151]
59. Babiker A, Cuzick J. A simple frailty model for family studies with covariates. Stat Med 1994;13:1679–92. [PubMed: 7973243]
60. Zhang H, Merikangas KR. A frailty model of segregation analysis: understanding the familial transmission of alcoholism. Biometrics 2000;56:815–23. [PubMed: 10985221]
61. Duncan T, Duncan S, Hops H. The role of parents and older siblings in predicting adolescent substance use: modeling development via structural equation latent growth methodology. J Fam Psychol 1996;10:158–72.

62. Luthar SS, Anton SF, Merikangas KR, Rounsaville BJ. Vulnerability to substance abuse and psychopathology among siblings of opioid abusers. J Nerv Ment Dis 1992;180:153–61. [PubMed: 1588332]

63. Rounsaville BJ, Kosten TR, Weissman MM, Prusoff B, Pauls D, Anton SF, et al. Psychiatric disorders in relatives of probands with opiate addiction. Arch Gen Psychiatry 1991;48:33–42. [PubMed: 1984760]

64. Agrawal A, Lynskey MT. The genetic epidemiology of cannabis use, abuse and dependence. Addiction 2006;101:801–12. [PubMed: 16696624]

65. Fu Q, Heath AC, Bucholz KK, Nelson E, Goldberg J, Lyons MJ, et al. Shared genetic risk of major depression, alcohol dependence, and marijuana dependence: contribution of antisocial personality disorder in men. Arch Gen Psychiatry 2002;59:1125–32. [PubMed: 12470129]

66. Nurnberger JI, Wiegand R, Bucholz K, O'Connor S, Meyer ET, Reich T, et al. A family study of alcohol dependence: coaggregation of multiple disorders in relatives of alcohol-dependent probands. Arch Gen Psychiatry 2004;61:1246–56. [PubMed: 15583116]

67. Khantizian EJ. The self-medication hypothesis of substance use disorders: a reconsideration and recent applications. Harv Rev Psychiatry 1997;4:231–44. [PubMed: 9385000]

68. Degenhardt L, Coffey C, Carlin JB, Swift W, Patton GC. Are diagnostic orphans at risk of developing cannabis abuse or dependence? Four-year follow-up of young adult cannabis users not meeting diagnostic criteria. Drug Alcohol Depend 2008;92:86–90. [PubMed: 17716830]

69. Degenhardt L, Lynskey M, Coffey C, Patton G. Diagnostic orphans' among young adult cannabis users: persons who report dependence symptoms but do not meet diagnostic criteria. Drug Alcohol Depend 2002;67:205–12. [PubMed: 12095670]

70. Grant BF, Pickering R. Cannabis use and DSM-IV cannabis use and dependence: results from the National Longitudinal Alcohol Epidemiologic Survey. J Subst Abuse 1999;10:255–64. [PubMed: 10689658]

71. Compton WM, Grant BF, Colliver JD. Prevalence of marijuana use disorders in the United States: 1991–1992 and 2001–2002. JAMA 2004;291:2114–21. [PubMed: 15126440]

72. Midanik LT, Greenfield TK, Bond J. Addiction sciences and its psychometrics: the measurement of alcohol-related problems. Addiction 2007;102:1701–10. [PubMed: 17610540]

73. Low NC, Cui L, Merikangas KR. Community versus clinic sampling: effect on the familial aggregation of anxiety disorders. Biol Psychiatry 2008;63:884–90. [PubMed: 17945198]

## Table 1

Characteristics of proband groups.

| Characteristic | Cannabis use disorder (n = 36) | Alcohol dependence (n = 89) | Anxiety disorders alone (n = 76) | Controls (n = 61) |
|---|---|---|---|---|
| Age (years) (mean) | 35.7 | 40.4 | 39.9 | 40.8 |
| Male (%) | 58.3 | 70.7 | 26.3 | 42.6 |
| Socio-economic status (mean) | 46.8 | 43.8 | 34.0 | 30.8 |
| Percentage employed | 86.1 | 82.0 | 80.3 | 88.5 |
| Household income (/$1000) (%) | | | | |
| <29 | 33.3 | 42.6 | 23.7 | 6.7 |
| 30–59 | 44.4 | 32.6 | 50.0 | 58.3 |
| 60+ | 22.2 | 23.5 | 26.3 | 35.0 |
| Religion (%) | | | | |
| Catholic | 52.8 | 57.3 | 58.7 | 57.4 |
| Protestant | 11.1 | 19.1 | 20.0 | 23.0 |
| Jewish | 2.8 | 1.1 | 4.0 | 9.8 |
| Other | 8.3 | 6.7 | 9.3 | 4.9 |
| Not affiliated | 25.0 | 15.7 | 8.0 | 4.9 |
| Education (%) | | | | |
| Partial university or higher | 38.9 | 47.7 | 63.1 | 78.7 |
| High school | 38.9 | 32.6 | 34.2 | 19.7 |
| Partial high school or lower | 22.2 | 19.1 | 2.6 | 1.6 |

## Table 2

Association of cannabis use disorders in probands, relatives and spouses.

| | Siblings > 18 | Offspring > 18 | Adult relatives | Spouses |
|---|---|---|---|---|
| **Cannabis use disorder in proband** | **n (% with cannabis use disorder)** | | | |
| Yes | 28 (25.7) | 4 (50.0) | 32 (27.4) | 15 (34.9) |
| No | 42 (8.2) | 15 (13.0) | 57 (9.1) | 22 (8.8) |
| Odds ratio (95% confidence intervals)[a] | 3.6 (2.0–6.5) | 6.9 (1.4–33.5) | 4.5 (2.6–7.6) | 4.4 (1.9–10.1) |

[a] Adjusted for sex and age of proband and relative.

**Table 3**

Factors associated with cannabis use disorders in probands and relatives.

| Variable | Estimate | SE | Odds ratio | 95% CI | P-value |
|---|---|---|---|---|---|
| Cannabis (latent familial factor) | 2.131 | 0.989 | 8.4 | 1.2–58.5 | * |
| Probands | | | | | |
| Sex (male versus female) | 0.654 | 0.472 | 1.9 | 0.8–4.9 | NS |
| Comorbidity (yes versus no) | | | | | |
| Anxiety | −0.300 | 0.350 | 0.7 | 0.4–1.5 | NS |
| Major depression | −0.059 | 0.329 | 0.9 | 0.5–1.7 | NS |
| Alcohol dependence | 0.948 | 0.372 | 2.6 | 1.2–5.4 | ** |
| Antisocial personality disorder | −0.813 | 0.599 | 0.4 | 0.1–1.4 | NS |
| Relatives | | | | | |
| Sex (male versus female) | −0.6 | 0.439 | 0.5 | 0.2–1.3 | NS |
| Age (increase/year) | 0.883 | 0.368 | 2.4 | 1.2–5.0 | * |
| Comorbidity (yes versus no) | | | | | |
| Anxiety | 0.400 | 0.339 | 1.5 | 0.8–2.9 | NS |
| Major depression | 0.447 | 0.384 | 1.6 | 0.7–3.3 | NS |
| Alcohol dependence | 1.460 | 0.385 | 4.3 | 2.0–9.2 | *** |
| Antisocial personality disorder | 1.308 | 0.535 | 3.7 | 1.3–10.6 | ** |
| Interview status (yes versus no) | −0.125 | 0.021 | 0.9 | 0.8–0.9 | *** |
| Sex of proband × sex of relative | −0.429 | 0.655 | 0.7 | 0.2–2.4 | NS |

Significance level: NS = not significant at 0.05;

* $P < 0.05$;

** $P < 0.01$;

*** $P < 0.001$. CI: confidence interval; SE: standard error.