Two-part random effects growth modeling to identify risks associated with alcohol and cannabis initiation, initial average use and changes in drug consumption in a sample of adult, male twins

Nathan A. Gillespie[a,b,*], **Gitta H. Lubke**[c], **Charles O. Gardner**[a], **Michael C. Neale**[a,d], and **Kenneth S. Kendler**[a,d]

[a]Department of Psychiatry, Virginia Commonwealth University, United States

[b]Queensland Institute of Medical Research, Brisbane, Australia

[c]Department of Psychology, University of Notre Dame, United States

[d]Department of Human Genetics, Virginia Commonwealth University, United States

Abstract

Aims—Our aim was to profile alcohol and cannabis initiation and to characterize the effects of developmental and environmental risk factors on changes in average drug use over time.

Design—We fitted a two-part random effects growth model to identify developmental and environmental risks associated with alcohol and cannabis initiation, initial average use and changes in average use.

Participants—1796 males aged 24–63 from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders.

Measurements—Data from three interview waves included self-report measures of average alcohol and cannabis use between ages 15 and 24, genetic risk of problem drug use, childhood environmental risks, personality, psychiatric symptoms, as well as personal, family and social risk factors.

Findings—Average alcohol and cannabis use were correlated at all ages. Genetic risk of drug use based on family history, higher sensation seeking, and peer group deviance predicted both alcohol and cannabis initiation. Higher drug availability predicted cannabis initiation while less parental monitoring and drug availability were the best predictors of how much cannabis individuals consumed over time.

Conclusion—The liability to initiate alcohol and cannabis, average drug use as well as changes in drug use during teenage years and young adulthood is associated with known risk factors.

Keywords

Alcohol; Cannabis; Initiation; Longitudinal; Risks; Two-part random effects; Latent class; Growth curve; Mixture distributions

---

1. Introduction

Alcohol and cannabis use disorders are complex traits influenced by genetic and environmental risks. Attempts to prevent use, avoid health and psychiatric consequences and identify prophylaxes (Degenhardt and Hall, 2002; Leweke and Koethe, 2008; Nurnberger et al., 2004) require distinguishing between processes that increase liability to drug use versus processes influencing patterns of use following initiation. Although genetic risks impact drug use and drug use disorders (Goodwin et al., 1973; Heath et al., 1997, 1991; Hettema et al., 1999; Kaprio et al., 1991; Pickens et al., 1991; Prescott et al., 1994; Prescott and Kendler, 1999; Sigvardsson et al., 1996), liability to alcohol and cannabis use can be predicted by a variety of social–environmental factors in early to mid-childhood (Caspi et al., 1996; Casswell et al., 2002; Chassin et al., 2002; Colder et al., 2002; Dubow et al., 2008; Ellickson et al., 2004; Englund et al., 2008; Jackson and Sher, 2006; Li et al., 2001; Maggs et al., 2008; Manzardo et al., 2005; Oxford et al., 2003; Pitkanen et al., 2008; Wiesner et al., 2007; Windle et al., 2005; Windle and Wiesner, 2004), personality dimensions (McGue et al., 1999), and externalizing behaviors (Boyle et al., 1992; Fergusson and Lynskey, 1998; Helzer et al., 1992; Lynskey and Fergusson, 1995; Szobot and Bukstein, 2008; Young et al., 1995). In addition, alcohol and cannabis use can be predicted during adolescence and teenage years by exposure to environmental risks and protective factors, e.g., parental monitoring (Dishion and Loeber, 1985b), childhood sexual or physical abuse (Fergusson and Mullen, 1999; Kendler et al., 2000a), parental attitudes toward drug use (McDermott, 1984), household drug use (Gfroerer, 1987), deviant peer group affiliation (Kandel et al., 1978), drug availability (Freisthler et al., 2005), participation in pro-social activities (Kendler et al., 1997; Werner, 1982; Werner and Smith, 1989). Yet despite the number of significant associations, it is unclear exactly how these risk factors covary with (i) the liability to use alcohol and cannabis and (ii) patterns of consumption following initiation.

When combining risks factors into a predictive developmental model, the distribution of the data must be taken into account. Although alcohol and cannabis are initiated on average by age 18 (Gillespie et al., 2009b; Wagner and Anthony, 2002), the distribution of initiation and average drug use at any given point remains semi-continuous. Such distributions have a characteristic histogram with a substantive proportion of zero responses along-side a skewed response pattern for the remainder of the response range. For cannabis, zero responders are high with lifetime abstinence among males of 46% (Gillespie et al., 2009b). Although the number of males who do not consume at least one full alcoholic drink in their lives is lower (3%) the proportion of zero responders only declines after adolescence so that abstemious subgroups can be observed in epidemiological samples (Kendler et al., 2008).

Therefore, our exploratory approach to unravel the role of risk factors over time is to fit a two-part random-effects model (Olsen and Schafer, 2001) which was specifically designed to take into account semi-continuous distributions. Specifically, the model assumes two processes underlie observed semi continuous responses. The first process is binary which differentiates between users and non-users, i.e., whether a response is zero or not. The second process is continuous and reflects the degree of use among drug users only. Both processes are modeled over time. At each time point, a zero response results in a zero for the first process and missing for the second process. In other words, non-users are not considered for modeling the second process. For users (non-zero responders), a latent

growth curve model is fitted to the continuous consumption measures. Importantly, both processes are evaluated at each time point, permitting subjects to switch between the two regimes over time, e.g., a subject may be a non-user at time one, user at time two, and a non-user again for the remaining periods. These two processes may be equivalent or qualitatively distinct, i.e., they covary with different genetic and environmental risk factors. Although this method cannot identify subtypes among drug users, it is computationally stable, appropriate for semi-continuous longitudinal data and allows comparisons between abstainers and drug users in terms of known risk factors over developmental time (Olsen and Schafer, 2001).

2. Methods

2.1. Sample and assessment procedures

As part of an ongoing study of adult male twins from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders (VATSPSUD) this report is based on data collected from three waves of interviews (1994–2004; Kendler and Prescott, 2006). Briefly, twins were eligible for participation if one or both were successfully matched to birth records, were a member of a multiple birth with at least one male, were Caucasian, and were born between 1940 and 1974. Of the 9417 eligible individuals for Wave 1 (1993–1996), 6814 (72.4%) completed the interview. This included 5074 males (the figure excludes third-born member of triplets) from 1499 complete and 2076 incomplete twin pairs (or singletons). Subjects who completed the Wave 1 interview were contacted approximately 1 yr later to schedule a second interview (1994–1998). Wave 2 was completed by 4203 (83%) males from 1189 complete twin pairs and 1825 singletons. A third interview targeting the complete male twin pairs who participated in Wave 2 was launched (2000–2004) to study the nature and pattern of risk and protective factors for psychoactive substance use (PSU) and psychoactive substance use disorders (PSUD) across adolescence and young adulthood. Wave 3 was completed by 1778 males (75%), aged 24–62 yrs ($\mu = 40.3$, SD = 9.0) from 745 complete twin pairs and 288 singletons.

At each wave the Committee for the Conduct of Human Research at Virginia Commonwealth University approved protocols given subjects along with a full explanation. Signed informed consents were obtained before all face-to-face interviews. Verbal assent was obtained before all telephone interviews. Most subjects were telephone interviewed. However, a small number were interviewed in person because of subject preference, residence in an institutional setting, or not having telephone service.

Interviewers possessed a master's degree in social work, psychology, another mental health related field, or a bachelor's degree in one of these areas plus a minimum of 2 yrs relevant clinical experience. They received 40 h of training plus regular individual and group review sessions. Two senior staff members reviewed interviews for completeness and consistency. Each member of a twin pair was interviewed by different interviewers blind to clinical information about the co-twin.

2.2. Model variables

After a systematic review of the literature, the 15 risk factors in Table 1 were selected because of previous significant associations with drug use and drug use disorders. Risks are divided into four developmental tiers reflecting: (i) genetic risks and year of birth; (ii) aspects of the childhood environment; (iii) critical temperamental and symptom variables; and (iv) key personal, social and environmental risk factors in late adolescence. The third interview included a number of retrospective assessments spanning five development periods (8–11 yrs, 12–14 yrs, 15–17 yrs, 18–21 yrs, and 22–25 yrs) to coincide with the timing of major developmental milestones, i.e., leaving the parental home, finishing school,

college entry and completion. Also included in the third interview were items assessing the period of "growing up" we defined as between the ages of 8 and 18 yrs.

2.3. Quality control and reliability

Because a number of the childhood environmental risks, temperamental and symptom variables, as well as personal, family and social risk factors measured at the Wave 3 interview are retrospective, these data are potentially contaminated by recall bias and telescoping effects our study used a Life History Calendar format developed by Thornton (Freedman et al., 1988) to improve the quality of the data. Empirically, this method has been shown to improve the accuracy of retrospective reporting by providing multiple cues to increase the chances of accurate recall (Belli, 1998). The method makes the task more akin to the accurate and well-retained process of recognition than to the less reliable task of free recall.

2.4. Genetic risks

Given significant heritability for alcohol and cannabis use (Heath et al., 1997; Kendler et al., 2000b; Kendler and Prescott, 1998; Lynskey et al., 2002; McGue et al., 2000; Miles et al., 2001; Pickens et al., 1991; Prescott et al., 1999; Prescott and Kendler, 1999; Rhee et al., 2003; van den Bree et al., 1998) we included estimates of individual genetic risk for problematic alcohol and cannabis use. These were based on Wave 2 interview self-reports asking twins to report on their paternal, maternal and cotwin's drug use. Specifically, the response distributions to three questions: (i) "Did your father ever have a problem with [drinking/cannabis] that lasted at least a month?"; (ii) "Did your mother ever have a problem with [drinking/cannabis] that lasted at least a month?"; and (iii) "Has your twin ever had a problem with [drinking/cannabis] that lasted at least a month?"

Genetic risks for problematic alcohol and cannabis use were calculated. For each of the three ordinal items, dichotomous responses (0 or 1) were translated using the SAS software program (SAS, 2006) into `relative to an identified distribution' or RIDIT scores which are deviations or expected values away from the mean of 0.5 under a uniform distribution (0–1) (Lehmann, 1975; van Elteren, 1960) e.g. a binary variable with prevalence rates of 40% and 60% (i.e. 0–40%, 40–100%) would be scored 0.2 and 0.7.

In the classical twin design, the additive genetic correlation for MZ twin pairs is fixed to 1.0, whereas the DZ twin pair correlation is 0.5 because the later on average share only half their genes in common. Accordingly, RIDIT scores for MZ twins reporting on their cotwin's drug use were unmodified from the uniform distribution compared to scores from DZ twins reporting on their cotwin which were adjusted half way back to a mean score of 0.5. By weighting the MZ scores twice as strongly as DZ scores this effectively reduces the uniform distribution for DZ twins from 0.0–1.0 to 0.25–0.75 to reflect the fact that MZ twin pairs are on average twice as genetically similar compared to DZ twin pairs. RIDIT scores for MZ and DZ twins reporting on maternal and paternal drug use were all adjusted half way back to a mean score of 0.5. This is because the parent–offspring genetic correlation is 0.5 regardless of whether offspring are MZ or DZ twins. Individual genetic risks were then calculated using the mean parental and cotwin RIDIT scores. Although this method provides an estimate of genetic risk, these scores include non-shared environmental variance that by definition must also include measurement error.

The same method was used to calculate a genetic risk for EXTERNALIZING DISORDERS based on: (i) co-twin's self-reports of DSM-IV (American Psychiatric Association, 1994) symptoms of *conduct disorder* (Wave 1 and Wave 2); (ii) subjects reporting on co-twin's DSM-IV symptoms of *antisocial personality disorder* (Wave 2); (iii) co-twin's self-reported

DSM-IV symptoms of *antisocial personality disorder* (Wave 2); and (iv) subjects reporting on father's symptoms of antisocial personality disorder (Wave 2) using the FH-RDC (Family History-Research Diagnostic Criteria; Lavori et al., 1988). Individual genetic risk was calculated as the mean RIDIT scores.

2.5. Childhood environmental risks

Based on two items measured at three retrospective periods (8–11 yrs, 12–14 yrs, and 15–17 yrs), CHURCH ATTENDANCE assessed how often subjects participated in church activities or youth groups ("*never,*" "*rarely,*" "*sometimes,*" and "*often*") and how often they attended religious services ("*more than once a week,*" "*once a week,*" "*a few times a month,*" "*once a month,*" "*less than once a month,*" and "*never*"). Reliability for this variable (intraclass correlation [ICC]) equaled +0.88. HOUSEHOLD DRUG USE was based on six items which asked how often tobacco, alcohol and drugs (marijuana and other drugs like cocaine and LSD) were used by someone other than the co-twin in the household from age eight until the subject left home. Response options were "*nearly every day*" "*once or twice a week*" "*a few times a month*" "*once or twice a year*" or "*never.*" Reliability (weighted kappa) equaled +0.78. PARENTAL ATTITUDES were based on seven items and asked subjects about the attitudes their parents had toward the use of tobacco, alcohol, and other drugs prior to age 18. Items included "*Is it OK for a teenage to smoke cigarettes?*" "*Is it OK for a teenager to get drunk?*" and "*Is it OK for a teenager to use marijuana?*". Response options were (would your parents) "*strongly agree,*" "*agree,*" "*disagree,*" "*strongly disagree*" or "*don't know.*" The reliability (weighted kappa) was +0.43. CHILDHOOD PHYSICAL or SEXUAL ABUSE was assessed with two items inquiring from the twin whether he had ever been "*sexually abused or molested*" before the age of 16 or "*physically abused as a child.*"

2.6. Temperamental and symptom variables

Symptoms of disruptive behavior were measured retrospectively at 15–17 yrs using 14 items based on the DSM-IV symptoms for Attention Deficit Hyperactive Disorder (11 items) and Oppositional Defiant Disorder (3 items). Reliability (ICC) equaled +0.81. Response options for items such as "*How often did you have difficulty staying seated*" were "*never,*" "*rarely,*" "*sometimes*" and "*often.*" NEUROTICISM was assessed by the Short-Scale version from the EPQ-R (73) scored as a five level ordinal measure. SENSATION-SEEKING was a continuous measure based on eleven items from the Sensation Seeking Scale. Reliability for this variable (ICC) equaled +0.81. EARLY ONSET ANXIETY DISORDER was a dichotomous variable scored for subjects with an onset before age 18 of panic disorder, generalized anxiety disorder or any form of phobia using diagnostic criteria outlined previously (Kendler and Prescott, 2006).

2.7. Personal, family and social risk factors in late adolescence

Symptoms of CONDUCT DISORDER between ages 15 and 17 yrs were measured using 11 items from the DSM-IV (American Psychiatric Association, 1994) and the Disruptive Behavior Disorders scale (Pelham and Murphy, 1995) that assessed aggression, deceitfulness, theft, rule violations and property destruction. Reliability (weighted kappa) equaled +0.59. Between ages 8 and 17 PARENTAL MONITORING between ages 8 and 17 yrs was assessed using 11 items based on previous work examining parental effects on risk of drug use and delinquency (Kerr and Stattin, 2000; Stattin and Kerr, 2000; Stattin and Romelsjo, 1995). Items asked subjects how much their parents or guardians knew who friends were, how they spent money, and what they did with free time, and knew where they were at night. Response options were (they) "*didn't know*" "*knew a little*" or "*knew a lot.*" Reliability (weighted kappa) equaled +0.69. PEER GROUP DEVIANCE between ages 15 and 17 yrs was assessed using 12 items based on two validated instruments (Johnston et al.,

1982; Tarter and Hegedus, 1991) that evaluated the proportion of the respondent's friends, who smoked, drunk alcohol, had problems with alcohol, had been in trouble with the law, stole or damaged property, smoked marijuana, used inhalants, used other drugs like cocaine, downers or LSD, and sold or gave drugs to other kids. Reliability (ICC) equaled +0.81. Finally, measures of ALCOHOL between ages 8 and 21 and CANNABIS AVAILABILITY between 8 and 25 yrs were assessed using a single item from the Monitoring the Future study (Bachman et al., 1996; Johnston et al., 1982) that asked subjects, at each retrospective period, how easy it would have been to get alcohol or cannabis if they wanted to use it. The response options were "*very easy*," "*somewhat easy*," "*somewhat difficult*" and "*very difficult*." Reliability (weighted kappa) equaled +0.58.

2.8. Alcohol and cannabis use

The third interview assessed average alcohol use in `standard' drink units that equaled one and one half ounces of spirits, six ounces of wine, or twelve ounces of beer. Average cannabis use was measured in individual drug units whereby one joint was considered one dose. Our modeling was based on average monthly use calculated at five two-year intervals from ages 15–24. Retest correlations adjusted for linear ages effects based on 142 subjects (mean interval = 29 days, range = 14–56 days) for the 6 intervals were 0.98, 0.91, 0.94, 0.95, 0.93 and 0.94 for cannabis and 0.81, 0.74, 0.84, 0.92, 0.93 and 0.86 for alcohol.

2.9. Marginal maximum likelihood risk factor scores

Except for genetic risks, physical or sexual abuse, and early onset anxiety disorder individual Maximum Likelihood factor scores were estimated for all other risk factors using the Mx software (Neale, 1999). Based on a single common factor model, this method isolates factor and item specific variance including measurement error for each risk factor in order to quantify more precisely each individual's risk (Schmitt et al., 2006).

2.10. Statistical analyses

For analysis of retrospective self-reported alcohol and cannabis use data we fitted Olsen and Schafer's (Olsen and Schafer, 2001) two-part random-effects model using the Mplus software (Muthén and Muthén, 1998–2001). Part one fits a latent class model to predict group membership in terms of users versus non-users. Zero values for `non-use' at each time point are assumed to include a mixed population of (i) structural zeroes or true abstainers and (ii) random cases of non-use for individuals who might otherwise use alcohol or cannabis. This latter subgroup of non-users can be identified by similarity of response patterns on covariates with users compared to true abstainers. Part two fits a growth curve model to estimate, among users over time, average drug use (intercept) and changes in average use (slope). An advantage of this model is that it permits subjects to switch between users and non-users, e.g., a subject may be a non-user at time one, user at time two, and a non-user again for the remaining time points. Central to our aim is the inclusion of proxies for developmental and environmental risk factors as covariates of drug use and consumption patterns. These covariates predict (i) latent class membership in terms of true abstainers versus drug users, (ii) initial average consumption (intercept) and (iii) changes in average consumption over time (slope).

The model was fitted to data comprising average drug use over five two-year intervals between 15 and 24 yrs. Although the analyses were run separately for alcohol and cannabis use, covariates were the same (except of genetic risk of problematic alcohol/cannabis use and alcohol/cannabis availability) in order to compare the patterns of significance and effect sizes across drugs. To adjust for correlated observations the analyses were clustered by family in Mplus (Muthén and Muthén, 1998–2001).

3. Results

Results for the two-part random effects models are shown in Table 2.

3.1. Alcohol

The risk factors combined explained 32%, 29% and 5%, respectively, of the variance in the risk of initiating initial average use, and the changes in average use over time. None of the childhood environmental risks predicted liability to alcohol initiation. Individuals with a high familial genetic risk for problem alcohol use who reported elevated sensation seeking, symptoms of conduct disorder and peer group deviance were more likely to initiate alcohol. Among these risks, peer group deviance had the largest effect ($\beta = 0.30$). Individuals who did not report an early onset anxiety disorder were also more likely to initiate. Following initiation, individuals at high genetic risk for problem alcohol use along with elevated conduct disorder and peer group deviance risk factor scores tended to report higher average alcohol consumption.

Unlike genetic risk for problem alcohol use, peer group deviance and to a lesser extent symptoms of conduct disorder that predicted both the risk of initiation and average alcohol use, risks such as sensation seeking and early onset anxiety disorder predicted initiation but not average use.

Although none of the childhood environmental risks predicted either alcohol initiation or initial average use, individuals who reported having parents with stronger attitudes against drug use ($\beta = -0.17$) reported lower changes in average use following initiation whereas individuals whose parents were more favorable toward drug use report higher changes in average consumption. However, because the correlation between initial average use and change in average use was negative ($r = -0.50_{SE=0.05}$, $p < 0.001$) this effect was more likely to be seen among subjects whose initial average consumption was low.

3.2. Cannabis

Developmental and environmental risk factors explained 42%, 51% and 26% of the variance in risk of cannabis use, initial average use, and changes in average use over time respectively. Specifically, subjects with high genetic risk for problem cannabis use, high genetic risk of externalizing disorder, high sensation seeking personalities, low parental monitoring, high peer group deviance, and who reported more cannabis availability were significantly more likely to initiate cannabis. Only high genetic risk for externalizing disorder, low parental monitoring, and high cannabis availability predicted both initiation and average use. This is in contrast to sensation seeking and peer group deviance, which predicted odds of initiating but not average use.

Cannabis availability was a significant predictor of cannabis initiation, average use and changes in use ($\beta = 0.36$ and 0.45 respectively). It was also significantly but negatively associated with changes in use ($\beta = -0.25$). Older subjects ($\beta = 0.30$) and those who had reported cannabis as having being more difficult to obtain ($\beta = -0.25$) tended to report greater changes in average cannabis consumption over time. However, because the correlation between initial average use and change in average use was again negative ($r = -0.50_{SE=0.08}$, $p < 0.001$) the larger change in average use among older individuals reporting less availability is likely to be seen more among subjects whose average consumption was low to begin with.

4. Discussion

Our exploratory analysis was designed to characterize how risk factors covary with alcohol and cannabis initiation, average use and changes in consumption. Compared to abstainers, alcohol and cannabis users have identifiable risk profiles broadly consistent with reports based on individuals sampled at similar age groups (Chassin et al., 2002; Ellickson et al., 2004; Windle et al., 2005; Windle and Wiesner, 2004). Genetic, personal, family, social and to a lesser extent childhood risk factors explain large proportions of the variance in the liability to initiate alcohol and cannabis use as well as the variance in initial average use and changes in average use. Some risks are drug specific. Others risk are common across substances while some of the factors that predict liability to initiate do not appear to predict measures of average use, and vice versa.

Our results indicate that those individuals who score highly on measures of genetic liability as indexed by family histories, sensation seeking, and peer group deviance tend to initiate both alcohol and cannabis. Although only marginally significant in the case of cannabis, genetic risk of problematic drug use also predicts higher levels of initial average drug use. These results are consistent with findings elsewhere (Allen et al., 2003; Schuckit, 2009; Staiger et al., 2007).

Correlations between average alcohol and cannabis use measures at each interval between 15 and 24 are high and range between 0.51 and 0.61. These correlations suggest that some of the common risks increase both the risk (although not at the same time) of initiation and quantity drug use (Jackson et al., 2008; Labouvie and White, 2002).

Specific mechanisms responsible for these observed correlations and similarities in the longitudinal consumption trajectories for alcohol and cannabis may be the result of individuals tending to adopt different peer or social networks. Indeed, significant life events such as marriage before age 30 have been associated with declines in overall drug consumption (Prescott and Kendler, 2001). Another possibility is that common risks arise from a shared diathesis of correlated genetic and environmental influences (Conrod et al., 2000; Damberg et al., 2001; Miles et al., 2001). Indirect evidence to support this comes from findings of comorbid alcohol, cannabis and other illicit drug use (Wagner and Anthony, 2002) as well as evidence identifying shared latent genetic and environmental influences across a number of drug use phenotypes (Kendler et al., 2007b, 2003b).

Concerning drug-specific risks, higher levels of conduct disorder or the absence of an early onset anxiety disorder uniquely predicts trying alcohol. Reporting more deviant peers predicts average alcohol consumption but not cannabis. A genetic risk of externalizing disorders and reporting greater cannabis availability seem only to predict the odds of trying cannabis. Following initiation, it is lack of parental monitoring and reporting greater cannabis availability that predict average cannabis use. Favorable parental attitudes toward general drug use predict more change in alcohol use. Similarly, reporting cannabis as being difficult to obtain is associated with a greater change in average use. Because the correlation between initial average use and change in use is negative for both substances, this effect is more likely to be seen among subjects whose initial average consumption is low to begin with. We speculate a ceiling effect whereby individuals whose starting point or initial average is high are less likely to increase their consumption over time.

Within each drug, certain risks predict initiation and not average use and vice versa. For alcohol, high sensation seeking and an episode of early onset anxiety strongly predict the risk of using but not average use, whereas for cannabis peer group deviance and (again) sensation seeking predict initiation but not average use. Parental attitudes toward drug use appear to have little bearing on the chances of initiating either alcohol or cannabis

consumption. Instead, they are more important for predicting changes in average alcohol consumption following initiation.

With respect to etiology, it is possible that drug-specific covariates risks account for some of the unshared variance between alcohol and cannabis use, or for aspects of the genetic and environmental influences known to be uncorrelated across drug use phenotypes (Kendler et al., 2007b, 2003b). Likewise, any risks that predict initiation but not average use may account for the proportion of genetic and environmental liability in drug initiation that does not overlap with measures of chronic use and abuse (Agrawal and Lynskey, 2006; Agrawal et al., 2005; Gillespie et al., 2009b).

An assumption implicit in many previous reports (Boyle et al., 1992; Dishion and Loeber, 1985a; Fergusson and Lynskey, 1998; Freisthler et al., 2005; Helzer et al., 1992; Kandel et al., 1978; Kendler et al., 1997; Lynskey and Hall, 2001; McDermott, 1984; McGue et al., 1999; Szobot and Bukstein, 2008; Werner, 1982; Werner and Smith, 1989; Young et al., 1995) is that the etiology of risks is entirely environmental and antecedent to drug use. Recent analyses using the same data have revealed that as adolescents and teenagers mature, genetic factors play an increasingly important role in the most risk factors, e.g., drug availability (Gillespie et al., 2007) and peer choice (Kendler et al., 2007a). As an example of how twin modeling can be used to elucidate causal processes underlying the liability to drug use, and consistent with a process of social selection, we have shown how genetic and environmental risks associated with cannabis can drive the propensity to affiliate with deviant peers (Gillespie et al., 2009a).

Our results also provide a profile of individuals unlikely to initiate alcohol or cannabis. Notwithstanding the genetic risks, individuals who report the lowest peer group deviance are least likely to initiate alcohol use, those reporting lowest drug availability are least likely to ever use cannabis. The beta coefficients for cannabis availability on initiation and average use suggest this risk may be an ideal candidate for interventions aimed at harm reduction and because common environmental or cultural factors can explain a large proportion of the liability to initiate and progress to cannabis abuse (Gillespie et al., 2009b) it is tempting to suggest that reducing availability might result in reduced cannabis use. However, it is important to consider that rates of cannabis initiation and cannabis use disorders are not necessarily higher in communities which have decriminalized in part or in full the possession or use of illicit substances (Donnelly et al., 1995; Korf, 2002; Reinarman et al., 2004), nor are rates lower in countries such as the United States which have severe penalties for drug possession and use (Schlosser, 2004). Thus, it is possible that those reporting least availability may do so because they have not been motivated to discover whether the drug can be obtained. In essence, reports of low availability may be inaccurate.

Contrary to previous findings (Fergusson and Mullen, 1999; Gfroerer, 1987; Kendler et al., 2000a, 1997, 2003a) we found that a number of risks are unassociated with alcohol or cannabis use. For instance, childhood environmental risks such as household drug use or physical or sexual abuse do not appear to be related to initiation or escalation. Likewise, the failure to demonstrate an effect for church attendance and disruptive behavior symptoms was surprising given their known association with drug use. Spearman correlations between church attendance (8–17 yrs) and average cannabis use for the five two-year intervals were significant and in the expected direction: –0.21 (8–11 yrs); –0.23 (12–14 yrs); –0.18 (15–17 yrs); –0.17 (18–21 yrs); and –0.15 (22–25 yrs). Correlations between the disruptive behavior factor score and cannabis use across the same five two-year intervals were likewise significant but lower: 0.13 (8–11 yrs); 0.13 (12–14 yrs); 0.17 (15–17 yrs); 0.16 (18–21 yrs); and 0.14 (22–25 yrs). As shown in Table 3, some of the Childhood Environmental and Temperamental and Symptom risk factors that did not predict cannabis initiation correlated

moderately with the genetic risk of externalizing disorder. Likewise, non-significant risk factors of alcohol use such as church attendance, physical or sexual abuse, disruptive behaviors, and neuroticism also show moderate correlations with the genetic risk of externalizing disorder.

Therefore, we removed the two genetic risks and age at interview before re-running the cannabis and alcohol models. For cannabis, we found that sensation seeking, parental monitoring, peer group deviance and cannabis availability remained significant. Among the changes, infrequent church attendance ($\beta = -0.07$, SE = 0.03, $p < 0.05$) and conduct disorder ($\beta = 0.13$, SE = 0.03, p < 0.001) were now associated with cannabis initiation. Conduct disorder also predicted higher levels of average cannabis use ($\beta = 0.11$, SE = 0.04, p < 0.01). We however, found no association between disruptive behavior and cannabis initiation or patterns of cannabis consumption. For alcohol, church attendance ($\beta = -0.07$, SE = 0.03, p < 0.05) and parental attitude toward household drug use ($\beta = 0.07$, SE = 0.03, p < 0.01) were now associated with alcohol initiation. The same parental attitudes also predicted changes in average alcohol use over time ($\beta = -0.10$, SE = 0.03, p < 0.01). Evidence from twin studies has shown that a large part of the association between conduct disorder and symptoms of cannabis dependence is indexed by environmental risks shared in common (True et al., 1999). Likewise, covariance between church attendance and drug use is in part explained by common social-environmental factors that reduce drug use at younger ages and genetically influenced temperamental factors that are protective against drug use in older twins (Kendler and Myers, 2009). We speculate that genetic and environmental risks predisposing to both cannabis use and externalizing disorders also index some of the variance in church attendance, conduct disorder and sensation seeking. However, because of the phenotypic overlap, the effect of church attendance, conduct disorder and personality on cannabis use are likely masked when genetic risks are first entered into the model.

4.1. Limitations

Although our modeling has shown how the liability to initiate alcohol and cannabis, initial average use and changes in use are related to certain risk factors, our findings must be interpreted in the context of five potential limitations. First, our data were drawn from White Virginian males. Although males have a higher prevalence of drug use (Kendler et al., 2002), previous analyses using the same data suggest that it is broadly representative of US males and does not differ from the general population in rates of psychopathology, drug use and abuse (Kendler et al., 2000b). Second, there may be cohort differences. The extent to which differences between users and non-users, or risks predicting average use, are a function of age is uncertain. Not only has the prevalence of cannabis been increasing but the average age of initiation has also been getting younger (McCabe et al., 2007). Third, with the exception of the genetic risks and early onset anxiety disorder, our factor score estimates assumed a uni-dimensional structure. Confirmatory factor analysis in Mx (Neale, 1999) revealed that a single factor structure provided a better fit than did the uncorrelated, two, or three factor models. Fourth, our model fitting was not exhaustive. However, we believe that that by modeling the semi-continuous distributions as a two-part random effects model was appropriate because it can integrate over developmental time a large number of diverse risk factors related to drug initiation and measures of average drug use. Other choices include linear growth models. However these assume that data are normally distributed and semi-parametric approaches will have likewise been unsatisfactory because they cannot distinguish between zero and non-zero responses (Olsen and Schafer, 2001; Zeger et al., 1988). The practice of excluding zeroes is also problematic because some individuals will be incorrectly identified as true abstainers when in reality our population likely consists of individuals who will be lifelong `abstainers' (Olsen and Schafer, 2001) or `structural zeros' (Carlin et al., 2001) and zeroes which capture random cases of non-use among individuals

who will use the drug at other times in their lives (Blozis et al., 2007). This second class of `zero users' is likely to be substantial among our adolescents, many of who may not have had the opportunity to indulge for reasons such as availability and exposure opportunity. We chose not to model mixture distributions or classes of drug users within the population of alcohol and cannabis users. Notwithstanding the computation difficulties, growth mixture modeling is often problematic because post-hoc class comparisons depend critically on correct class assignment that is often unreliable (Lubke and Muthen, 2007; Tueller and Lubke, in press) unless appropriately weighted (Anderson et al., 2009; Barker and Maughan, 2009).

Acknowledgments

References

Agrawal A, Lynskey MT. The genetic epidemiology of cannabis use, abuse and dependence. Addiction. 2006; 101:801–812. [PubMed: 16696624]

Agrawal A, Neale MC, Jacobson KC, Prescott CA, Kendler KS. Illicit drug use and abuse/dependence: modeling of two-stage variables using the CCC approach. Addict. Behav. 2005; 30:1043–1048. [PubMed: 15893102]

Allen M, Donohue WA, Griffin A, Ryan D, Turner MM. Comparing the influence of parents and peers on the choice to use drugs. Crim. Justice Behav. 2003; 30:163–186.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV. American Psychiatric Association; Washington, DC: 1994.

Anderson KG, Ramo DE, Cummins KM, Brown SA. Alcohol and drug involvement after adolescent treatment and functioning during emerging adulthood. Drug Alcohol Depend. 2009; 107:171–181. [PubMed: 19926231]

Bachman, JG.; Johnston, LD.; O'Malley, PM. Institute for Social Research. University of Michigan; Ann Arbor, Michigan: 1996. The Monitoring the Future Project after Twenty-two Years: Design and Procedures; p. 1

Barker ED, Maughan B. Differentiating early-onset persistent versus childhood-limited conduct problem youth. Am. J. Psychiatry. 2009; 166:900–908. [PubMed: 19570930]

Belli RF. The structure of autobiographical memory and the event history calendar: potential improvements in the quality of retrospective reports in surveys. Memory. 1998; 6:383–406. [PubMed: 9829098]

Blozis SA, Feldman B, Conger RD. Adolescent alcohol use and adult alcohol disorders: a two-part random-effects model with diagnostic outcomes. Drug Alcohol Depend. 2007; 88:S85–S96. [PubMed: 17280801]

Boyle MH, Offord DR, Racine YA, Szatmari P, Fleming JE, Links PS. Predicting substance use in late adolescence: results from the Ontario Child Health Study follow-up. Am. J. Psychiatry. 1992; 149:761–767. [PubMed: 1590492]

Carlin JB, Wolfe R, Brown CH, Gelman A. A case study on the choice, interpretation and checking of multilevel models for longitudinal binary outcomes. Biostatistics. 2001; 2:397–416. [PubMed: 12933632]

Caspi A, Moffitt TE, Newman DL, Silva PA. Behavioral observations at age 3 years predict adult psychiatric disorders. Longitudinal evidence from a birth cohort. Arch. Gen. Psychiatry. 1996; 53:1033. [PubMed: 8911226]

Casswell S, Pledger M, Pratap S. Trajectories of drinking from 18 to 26 years: identification and prediction. Addiction. 2002; 97:1427–1437. [PubMed: 12410783]

Chassin L, Pitts SC, Prost J. Binge drinking trajectories from adolescence to emerging adulthood in a high-risk sample: predictors and substance abuse outcomes. J. Consult. Clin. Psychol. 2002; 70:67–78. [PubMed: 11860058]

Colder CR, Campbell RT, Ruel E, Richardson JL, Flay BR. A finite mixture model of growth trajectories of adolescent alcohol use: predictors and consequences. J. Consult. Clin. Psychol. 2002; 70:485–976.

Conrod PJ, Pihl RO, Stewart SH, Dongier M. Validation of a system of classifying female substance abusers on the basis of personality and motivational risk factors for substance abuse. Psychol. Addict. Behav. 2000; 14:243. [PubMed: 10998950]

Damberg M, Garpenstrand H, Hallman J, Oreland L. Genetic mechanisms of behavior—don't forget about the transcription factors. Mol. Psychiatry. 2001; 6:503. [PubMed: 11526464]

Degenhardt L, Hall W. Cannabis and psychosis. Curr. Psychiatry Rep. 2002; 4:191–196. [PubMed: 12003681]

Dishion TJ, Loeber R. Adolescent marijuana and alcohol use: the role of parents and peers revisited. Am. J. Drug Alcohol Abuse. 1985a; 11:11. [PubMed: 4061428]

Dishion TJ, Loeber R. Adolescent marijuana and alcohol use: the role of parents and peers revisited. Am. J. Drug Alcohol Abuse. 1985b; 11:11–25. [PubMed: 4061428]

Donnelly N, Hall W, Christie P. The effects of partial decriminalisation on cannabis use in South Australia, 1985 to 1993. Aust. J. Public Health. 1995; 19:281–287. [PubMed: 7626679]

Dubow EF, Boxer P, Huesmann LR. Childhood and adolescent predictors of early and middle adulthood alcohol use and problem drinking: the Columbia County Longitudinal Study. Addiction. 2008; 103(Suppl. 1):36–47. [PubMed: 18426539]

Ellickson PL, Martino SC, Collins RL. Marijuana use from adolescence to young adulthood: multiple developmental trajectories and their associated outcomes. Health Psychol. 2004; 23:299–307. [PubMed: 15099171]

Englund MM, Egeland B, Oliva EM, Collins WA. Childhood and adolescent predictors of heavy drinking and alcohol use disorders in early adulthood: a longitudinal developmental analysis. Addiction. 2008; 103(Suppl. 1):23–35. [PubMed: 18426538]

Fergusson DM, Lynskey MT. Conduct problems in childhood and psychosocial outcomes in young adulthood: a prospective study. J. Emot. Behav. Dev. 1998; 6:2–18.

Fergusson, DM.; Mullen, PE. Childhood Sexual Abuse: An Evidence Based Perspective. Sage Publications, Inc.; Thousand Oaks, CA: 1999.

Freedman D, Thornton A, Camburn D, Alwin D, Young-DeMarco L. The life history calendar: a technique for collecting retrospective data. Sociol. Methodol. 1988; 18:37. [PubMed: 12282712]

Freisthler B, Needell B, Gruenewald PJ. Is the physical availability of alcohol and illicit drugs related to neighborhood rates of child maltreatment? Child Abuse Negl. 2005; 29:1049–1060. [PubMed: 16168479]

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]

Gillespie NA, Neale MC, Jacobson K, Kendler KS. Modeling the genetic and environmental association between peer group deviance cannabis use in male twins. Addiction. 2009a; 104:420–429. [PubMed: 19207350]

Gillespie NA, Neale MC, Kendler KS. Pathways to cannabis abuse: a multi-stage model from cannabis availability, cannabis initiation, and progression to abuse. Addiction. 2009b; 104:430–438. [PubMed: 19207351]

Gillespie NA, Prescott CA, Aggen SH, Gardner CO Jr. Jacobson K, Kendler KS, Neale MC. Longitudinal modelling of genetic and environmental influences on availability of psychoactive substances: alcohol, cigarettes, marijuana, cocaine and stimulants. Psychol. Med. 2007; 37:947–959. [PubMed: 17445283]

Goodwin DW, Schulsinger F, Hermansen L, Guze SB, Winokur G. Alcohol problems in adoptees raised apart from alcoholic biological parents. Arch. Gen. Psychiatry. 1973; 28:238–243. [PubMed: 4684290]

Heath AC, Bucholz KK, Madden PA, Dinwiddie SH, Slutske WS, Bierut LJ, Statham DJ, Dunne MP, Whitfield JB, Martin NG. Genetic and environmental contributions to alcohol dependence risk in a national twin sample: consistency of findings in women and men. Psychol. Med. 1997; 27:1381–1396. [PubMed: 9403910]

Heath AC, Meyer J, Eaves LJ, Martin NG. The inheritance of alcohol consumption patterns in a general population twin sample: I. multidimensional scaling of quantity/frequency data. J. Stud. Alcohol. 1991; 52:345–352. [PubMed: 1875708]

Helzer, JE.; Bucholz, KK.; Robins, LN. Results of the epidemiologic catchment area survey. In: Helzer, JE.; Canino, GJ., editors. Alcoholism in North America Europe and Asia. Oxford University Press; New York: 1992.

Hettema JM, Corey LA, Kendler KS. A multivariate genetic analysis of the use of tobacco, alcohol, and caffeine in a population based sample of male and female twins. Drug Alcohol Depend. 1999; 57:69–78. [PubMed: 10617315]

Jackson KM, Sher KJ. Comparison of longitudinal phenotypes based on number and timing of assessments: a systematic comparison of trajectory approaches II. Psychol. Addict. Behav. 2006; 20:373–384. [PubMed: 17176172]

Jackson KM, Sher KJ, Schulenberg JE. Conjoint developmental trajectories of young adult substance use. Alcohol. Clin. Exp. Res. 2008; 32:723–737. [PubMed: 18331376]

Johnston, LD.; Bachman, JG.; O'Malley, PM. Monitoring the Future: Questionnaire Responses from the Nation's High School Seniors, 1981. Institute for Social Research; Ann Arbor, MI: 1982.

Kandel DB, Kessler RC, Margulies RS. Antecedents of adolescent initiation into stages of drug use: a developmental analysis. J. Youth Adolesc. 1978; 7:13.

Kaprio J, Rose RJ, Romanov K, Koskenvuo M. Genetic and environmental determinants of use and abuse of alcohol: the Finnish Twin Cohort studies. Alcohol Alcohol. 1991; (Suppl. 1):131–136.

Kendler KS, Bulik CM, Silberg J, Hettema JM, Myers J, Prescott CA. Childhood sexual abuse and adult psychiatric and substance use disorders in women: an epidemiological and cotwin control analysis. Arch. Gen. Psychiatry. 2000a; 57:953–959. [PubMed: 11015813]

KendlerF KS, Gardner CO, Prescott CA. Religion, psychopathology, and substance use and abuse; a multimeasure, genetic-epidemiologic study. Am. J. Psychiatry. 1997; 154:322–329. [PubMed: 9054778]

Kendler KS, Gardner CO Jr. Gillespie NA, Jacobson K, Aggen SH, Prescott CA. Creating a social world: a developmental twin study of peer group deviance. Ann. Gen. Psychiatry. 2007a; 64:958–965.

Kendler KS, Karkowski LM, Neale MC, Prescott CA. Illicit psychoactive substance use, heavy use, abuse, and dependence in a US population-based sample of male twins. Arch. Gen. Psychiatry. 2000b; 57:261–269. [PubMed: 10711912]

Kendler KS, Liu XQ, Gardner CO, McCullough ME, Larson D, Prescott CA. Dimensions of religiosity and their relationship to lifetime psychiatric and substance use disorders. Am. J. Psychiatry. 2003a; 160:496–503. [PubMed: 12611831]

Kendler KS, Myers J. A developmental twin study of church attendance and alcohol and nicotine consumption: a model for analyzing the changing impact of genes and environment. Am. J. Psychiatry. 2009; 166:1150–1155. [PubMed: 19755576]

Kendler KS, Myers J, Prescott CA. The specificity of genetic and environmental risk factors for symptoms of cannabis, cocaine, alcohol, caffeine and nicotine dependence. Ann. Gen. Psychiatry. 2007b; 64:1313–1320.

Kendler KS, Neale MC, Thornton LM, Aggen SH, Gilman SE, Kessler RC. Cannabis use in the last year in a US national sample of twin and sibling pairs. Psychol. Med. 2002; 32:551–554. [PubMed: 11990000]

Kendler KS, Prescott CA. Cannabis use, abuse, and dependence in a population-based sample of female twins. Am. J. Psychiatry. 1998; 155:1016. [PubMed: 9699687]

Kendler, KS.; Prescott, CA. Genes, Environment, and Psychopathology: Understanding the Causes of Psychiatric and Substance Use Disorders. The Guilford Press; New York: 2006.

Kendler KS, Prescott CA, Myers J, Neale MC. The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. Arch. Gen. Psychiatry. 2003b; 60:929–937. [PubMed: 12963675]

Kendler KS, Schmitt E, Aggen SH, Prescott CA. Genetic and environmental influences on alcohol, caffeine, cannabis, and nicotine use from early adolescence to middle adulthood. Arch. Gen. Psychiatry. 2008; 65:674–682. [PubMed: 18519825]

Kerr M, Stattin H. What parents know, how they know it, and several forms of adolescent adjustment: further support for a reinterpretation of monitoring. Dev. Psychol. 2000; 36:366–380. [PubMed: 10830980]

Korf DJ. Dutch coffee shops and trends in cannabis use. Addict. Behav. 2002; 27:851–866. [PubMed: 12369472]

Labouvie, E.; White, HR. Drug sequences, age of onset, and use trajectories as predictors of drug abuse/dependence in young adulthood. In: Kandel, DB., editor. Stages and Pathways of Drug Involvement: Examining the Gateway Hypothesis. Cambridge University Press; Cambridge, UK: 2002.

Lavori PW, Keller MB, Endicott J. Improving the validity of FH-RDC diagnosis of major affective disorder in uninterviewed relatives in family studies: a model based approach. J. Psychiatr. Res. 1988; 22:249–259. [PubMed: 3216343]

Lehmann, EL. Nonparametrics: Statistical Methods Based on Ranks. Holden-Day; San Fransisco: 1975.

Leweke FM, Koethe D. Cannabis and psychiatric disorders: it is not only addiction. Addict. Biol. 2008; 13:264–275. [PubMed: 18482435]

Li F, Duncan TE, Hops H. Examining developmental trajectories in adolescent alcohol use using piecewise growth mixture modeling analysis. J. Stud. Alcohol. 2001; 62:199–210. [PubMed: 11327186]

Lubke G, Muthen BO. Performance of factor mixture models as a function of model size, covariate effects, and class-specific parameters. Struct. Equ. Model. 2007; 14:26–47.

Lynskey MT, Fergusson DM. Childhood conduct problems, attention deficit behaviors, and adolescent alcohol, tobacco, and illicit drug use. J. Abnorm. Child Psychol. 1995; 23:281–302. [PubMed: 7642838]

Lynskey MT, Hall W. Attention deficit hyperactivity disorder and substance use disorders: is there a causal link? Addiction. 2001; 96:815–822. [PubMed: 11399213]

Lynskey MT, Heath AC, Nelson EC, Bucholz KK, Madden PA, Slutske WS, Statham DJ, Martin NG. Genetic and environmental contributions to cannabis dependence in a national young adult twin sample. Psychol. Med. 2002; 32:195–207. [PubMed: 11871371]

Maggs JL, Patrick ME, Feinstein L. Childhood and adolescent predictors of alcohol use and problems in adolescence and adulthood in the National Child Development Study. Addiction. 2008; 103(Suppl. 1):7–22. [PubMed: 18426537]

Manzardo AM, Penick EC, Knop J, Nickel E, Hall S, Jensen P, Gabrielli WF Jr. Developmental differences in childhood motor coordination predict adult alcohol dependence: proposed role for the cerebellum in alcoholism. Alcohol. Clin. Exp. Res. 2005; 29:353–357. [PubMed: 15770110]

McCabe SE, West BT, Wechsler H. Trends and college-level characteristics associated with the non-medical use of prescription drugs among US college students from 1993 to 2001. Addiction. 2007; 102:455–465. [PubMed: 17298654]

McDermott D. The relationship of parental drug use and parents' attitude concerning adolescent drug use to adolescent drug use. Adolescence. 1984; 19:89. [PubMed: 6731072]

McGue M, Elkins I, Iacono WG. Genetic and environmental influences on adolescent substance use and abuse. Am. J. Med. Genet. 2000; 96:671–677. [PubMed: 11054776]

McGue M, Slutske WS, Iacono WG. Personality and substance use disorders: II. Alcoholism versus drug use disorders. J. Consult. Clin. Psychol. 1999; 67:394–404. [PubMed: 10369060]

Miles DR, van den Bree MB, Gupman AE, Newlin DB, Glantz MD, Pickens RW. A twin study on sensation seeking, risk taking behavior and marijuana use. Drug Alcohol Depend. 2001; 62:57–68. [PubMed: 11173168]

Muthén, LK.; Muthén, BO. Mplus User's Guide. Second ed.. Muthén & Muthén; Los Angeles, CA: 1998–2001.

Neale, MC. Mx: Statistical Modelling. fifth ed.. Medical College of Virginia; Richmond: 1999.

Nurnberger JI Jr. Wiegand R, Bucholz K, O'Connor S, Meyer ET, Reich T, Rice J, Schuckit M, King L, Petti T, Bierut L, Hinrichs AL, Kuperman S, Hessel-brock V, Porjesz B. A family study of alcohol dependence: coaggregation of multiple disorders in relatives of alcohol-dependent probands. Arch. Gen. Psychiatry. 2004; 61:1246. [PubMed: 15583116]

Olsen MK, Schafer JL. A two-part random-effects model for semicontinuous longitudinal data. J. Am. Stat. Assoc. 2001; 96:730–745.

Oxford ML, Gilchrist LD, Morrison DM, Gillmore MR, Lohr MJ, Lewis SM. Alcohol use among adolescent mothers: heterogeneity in growth curves, predictors, and outcomes of alcohol use over time. Prev. Sci. 2003; 4:15–26. [PubMed: 12611416]

Pelham, W.; Murphy, D. The DBD Rating Scale: A Parent and Teacher Rating Scale for the Disruptive Behavior Disorders of Childhood in DSM-III-R. Department of Psychiatry, University of Pittsburgh School of Medicine; 1995. unpublished

Pickens RW, Svikis DS, McGue M, Lykken DT, Heston LL, Clayton PJ. Heterogeneity in the inheritance of alcoholism. A study of male and female twins. Arch. Gen. Psychiatry. 1991; 48:19–28. [PubMed: 1984758]

Pitkanen T, Kokko K, Lyyra AL, Pulkkinen L. A developmental approach to alcohol drinking behaviour in adulthood: a follow-up study from age 8 to age 42. Addiction. 2008; 103(Suppl. 1): 48–68. [PubMed: 18426540]

Prescott CA, Aggen SH, Kendler KS. Sex differences in the sources of genetic liability to alcohol abuse and dependence in a population-based sample of U.S. twins. Alcohol. Clin. Exp. Res. 1999; 23:1136–1144. [PubMed: 10443978]

Prescott CA, Hewitt JK, Heath AC, Truett KR, Neale MC, Eaves LJ. Environmental and genetic influences on alcohol use in a volunteer sample of older twins. J. Stud. Alcohol. 1994; 55:18–33. [PubMed: 8189722]

Prescott CA, Kendler KS. Genetic and environmental contributions to alcohol abuse and dependence in a population-based sample of male twins. Am. J. Psychiatry. 1999; 156:34–40. [PubMed: 9892295]

Prescott CA, Kendler KS. Associations between marital status and alcohol consumption in a longitudinal study of female twins. J. Stud. Alcohol. 2001; 62:589–604. [PubMed: 11702798]

Reinarman C, Cohen PD, Kaal HL. The limited relevance of drug policy: cannabis in Amsterdam and in San Francisco. Am. J. Public Health. 2004; 94:836–842. [PubMed: 15117709]

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; 60:1256–1264. [PubMed: 14662558]

SAS Institute Inc.. Base SAS ® 9.1.3 Procedures Guide. Second Edition. Vol. Volumes 1, 2, 3, and 4. SAS Institute Inc.; Cary, NC: 2006.

Schlosser, E. Reefer Madness: Sex, Drugs, and Cheap Labour in the American Black Market. Mariner Books; New York: 2004.

Schmitt JE, Mehta PD, Aggen SH, Kubarych TS, Neale MC. Semi-nonparametric methods for detecting latent non-normality: a fusion of latent trait and ordered latent class modeling. Multivariate Behav. Res. 2006; 41:427–443.

Schuckit MA. An overview of genetic influences in alcoholism. J. Subst. Abuse Treat. 2009; 36:S5–S14. [PubMed: 19062348]

Sigvardsson S, Bohman M, Cloninger CR. Replication of the Stockholm Adoption Study of Alcoholism. Confirmatory cross-fostering analysis. Arch. Gen. Psychiatry. 1996; 53:681–687. [PubMed: 8694681]

Staiger PK, Kambouropoulos N, Dawe S. Should personality traits be considered when refining substance misuse treatment programs? Drug Alcohol Rev. 2007; 26:17–23. [PubMed: 17364832]

Stattin H, Kerr M. Parental monitoring: a reinterpretation. Child Dev. 2000; 71:1072–1085. [PubMed: 11016567]

Stattin H, Romelsjo A. Adult mortality in the light of criminality, substance abuse, and behavioral and family-risk factors. Crim. Behav. Ment. Health. 1995; 5:279–311.

Szobot CM, Bukstein O. Attention deficit hyperactivity disorder and substance use disorders. Child Adolesc. Psychiatr. Clin. N. Am. 2008; 17:309–323. viii. [PubMed: 18295148]

Tarter RE, Hegedus AM. The drug use screening inventory: its application in the evaluation and treatment of alcohol and drug abuse. Alcohol Health Res. World. 1991; 15:65–75.

True WR, Heath AC, Scherrer JF, Xian H, Lin N, Eisen SA, Lyons MJ, Goldberg J, Tsuang MT. Interrelationship of genetic and environmental influences on conduct disorder and alcohol and marijuana dependence symptoms. Am. J. Med. Genet. 1999; 88:391–397. [PubMed: 10402507]

Tueller S, Lubke GH. Evaluation of structural equation mixture models in a cross sectional setting: parameter estimates and correct class assignment. Struct. Equ. Model. in press.

van den Bree MB, Johnson EO, Neale MC, Pickens RW. Genetic and environmental influences on drug use and abuse/dependence in male and female twins. Drug Alcohol Depend. 1998; 52:231–241. [PubMed: 9839149]

van Elteren PH. On the combination of independent two-sample tests of Wilcoxon. Bull. Int. Stat. Inst. 1960; 37:351–361.

Wagner FA, Anthony JC. Into the world of illegal drug use: exposure opportunity and other mechanisms linking the use of alcohol, tobacco, marijuana, and cocaine. Am. J. Epidemiol. 2002; 155:918. [PubMed: 11994231]

Werner, E. Vulnerable but Invincible. McGraw-Hill; New York: 1982.

Werner, EW.; Smith, RS. Vulnerable but Invincible: A Longitudinal Study of Resilient Children and Youth. Adams Bannister Cox; New York: 1989.

Wiesner M, Weichold K, Silbereisen RK. Trajectories of alcohol use among adolescent boys and girls: identification, validation, and sociodemographic characteristics. Psychol. Addict. Behav. 2007; 21:62–75. [PubMed: 17385956]

Windle M, Mun EY, Windle RC. Adolescent-to-young adulthood heavy drinking trajectories and their prospective predictors. J. Stud. Alcohol. Drugs. 2005; 66:313–322.

Windle M, Wiesner M. Trajectories of marijuana use from adolescence to young adulthood: predictors and outcomes. Dev. Psychopathol. 2004; 16:1007–1027. [PubMed: 15704825]

Young SE, Mikulich SK, Goodwin MB, Hardy J, Martin CL, Zoccolillo MS, Crowley TJ. Treated delinquent boys' substance use: onset, pattern, relationship to conduct and mood disorders. Drug Alcohol Depend. 1995; 37:149–162. [PubMed: 7758404]

Zeger SL, Liang KY, Albert PS. Models for longitudinal data: a generalized estimating equation approach. Biometrics. 1988; 44:1049–1060. [PubMed: 3233245]

Table 1

Summary of risk factors measured at the first(1993-1993), second (1994–1998) and third (2000–2004) interviews. The third interview included retrospective assessments spanning five development periods (8–11 yrs, 12–14 yrs, 15–17 yrs, 18–21 yrs, and 22–25 yrs).

Risk factors	Scales	Wave
Genetic risk		
Alcohol|illicit drug problem	DSM-IV (115)	2
Externalizing disorder	DSM-IV (115), FH-RDC (71)	1,2
Childhood environmental risks		
Church attendance at 8–17 yrs[FS]	Monitoring the Future (80, 81)	3
Household drug use[a,FS]		3
Parental attitudes toward drugs[a,FS]	Monitoring the Future (80, 81)	3
Physical or sexual abuse		1
Temperamental and symptom		
Disruptive behavior at 15–17 yrs[b,FS]	DSM-IV (115)	3
Neuroticism[FS]	EPQ-R (116)	1
Sensation seeking[FS]	Sensation Seeking Scale (117)	3
Early onset anxiety disorder	DSM-IV (115)	2
Personal, family and social risks		
Conduct disorder at 15–17 yrs[FS]	DSM-IV (115), DBD Scale (75)	3
Parental monitoring[a,FS]	Stattin (76), Kerr (78)	3
Peer group deviance at 15–17 yrs[FS]	Tarter (79), Johnston (80)	3
Alcohol/cannabis availability 8–25 yrs[FS]	Monitoring the Future (80, 81)	3

Note: FH-RDC = Family History - Research Diagnostic Criteria, EPQ-R=Eysenck Personality Questionnaire - Revised, DBD = Disruptive Behavior Disorders.

[FS] Individual Marginal Maximum Likelihood factor score calculated based on a single principle component.

[a] Retrospective assessment period of "growing up" defined as ages 8–17 yrs or until left home.

[b] Based on attention deficit, hyperactivity disorder and oppositional defiance disorder psychiatric criterion.

Table 2

The effect of developmental and environmental risk factors in the prediction of alcohol and cannabis initiation, initial average use, and changes in average use over time. Results based on standardized beta (β) coefficients with standard errors (SE) from the two-part random effects model. Significant betas are bolded.

Risk factors	Alcohol						Cannabis					
	Odds of initiating		Initial average use		Changes in average use		Odds of initiating		Initial average use		Changes in average use	
	β (SE)	p	β (SE)	p	β (SE)	p	β (SE)	p	β (SE)	p	β (SE)	p
Age at interview	−.07 (.03)	.057	−.01 (.01)	.050	.01 (.01)	.108	.01 (.03)	.867	−.05 (.07)	.507	**.30 (.10)**	**.002**
Genetic risk factors												
Alcohol|cannabis	**.12 (.04)**	**.001**	**.16 (.03)**	**.000**	−.04 (.05)	.379	**.13 (.03)**	**.000**	.08 (.04)	.050	.09 (.06)	.137
Externalizing disorder	.04 (.04)	.331	.05 (.04)	.301	.02 (.06)	.767	**.13 (.04)**	**.002**	**.12 (.06)**	**.043**	−.03 (.10)	.779
Childhood environmental												
Church Attendance 8–17 yrs	−.06 (.04)	.092	−.05 (.04)	.207	.01 (.05)	.882	−.02 (.04)	.615	−.01 (.06)	.846	−.07 (.09)	.455
Household drug use	.02 (.04)	.550	.13 (.08)	.118	−.01 (.10)	.897	.06 (.04)	.095	.07 (.06)	.229	−.05 (.08)	.534
Parental Attitudes toward drugs	.05 (.04)	.208	.06 (.05)	.265	**−.17 (.06)**	**.006**	.02 (.04)	.570	−.08 (.05)	.119	.04 (.07)	.595
Physical or sexual abuse	−.06 (.03)	.070	−.16 (.15)	.285	−.01 (.17)	.947	.02 (.03)	.546	−.05 (.04)	.273	.05 (.06)	.478
Temperamental and symptom												
Disruptive behavior 15–17 yrs	−.01 (.04)	.814	.02 (.05)	.725	−.06 (.06)	.302	−.06 (.04)	.131	.00 (.05)	.947	.02 (.08)	.799
Neuroticism	.01 (.04)	.711	.00 (.05)	.938	.03 (.07)	.695	.00 (.04)	.959	.01 (.06)	.902	−.05 (.10)	.614
Sensation seeking	**−.10 (.04)**	**.004**	.05 (.04)	.193	.04 (.05)	.388	**.09 (.04)**	**.017**	.03 (.05)	.597	.09 (.08)	.246
Early onset anxiety disorder	**−.11 (.04)**	**.002**	−.01 (.11)	.963	.13 (.13)	.294	−.04 (.04)	.264	−.01 (.05)	.875	−.03 (.08)	.742
Personal, family and social												
Conduct disorder 15–17 yrs	**−.11 (.05)**	**.025**	**−.11 (.05)**	**.031**	−.09 (.06)	.159	.06 (.04)	.190	.01 (.06)	.821	−.02 (.08)	.840
Parental monitoring	−.07 (.04)	.052	−.08 (.05)	.080	.03 (.06)	.534	**−.11 (.04)**	**.005**	**−.25 (.06)**	**.000**	.15 (.10)	.124
Peer group deviance 15–17 yrs	**−.30 (.04)**	**.000**	**.17 (.04)**	**.000**	−.02 (.05)	.708	**.13 (.05)**	**.007**	.04 (.07)	.535	−.05 (.09)	.626
Alcohol|cannabis availability	.04 (.04)	.237	.08 (.05)	.122	−.04 (.07)	.609	**.36 (.04)**	**.000**	**.45 (.08)**	**.000**	**−.25 (.12)**	**.034**

Note: Models were fitted in Mplus using 15 abscissae for integration to balance the need for computational speed and optimal model convergence.

Table 3

Phenotypic polychoric correlations between risk factors based on the 2-part random effects models for cannabis (below diagonal) and alcohol (above diagonal).

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.
1. GR alcohol|cannabis	1	0.34	0.00	−0.07	0.14	0.09	0.08	0.13	0.16	0.06	0.09	0.15	−0.19	0.16	0.16
2. GR externalizing disorder	0.31	1	−0.08	−0.22	0.13	0.10	0.18	0.33	0.20	0.16	0.19	0.50	−0.33	0.30	0.23
3. Age at interview	−0.03	−0.08	1	0.21	−0.09	−0.02	0.01	−0.02	0.00	−0.23	−0.05	−0.13	0.13	−0.22	−0.13
4. Church attendance 8–17 yrs	−0.09	−0.22	0.20	1	−0.19	−0.26	−0.03	−0.08	−0.08	−0.13	−0.05	−0.16	0.28	−0.23	−0.26
5. Household drug use	0.07	0.13	−0.09	−0.19	1	0.18	0.02	0.09	0.02	0.10	0.03	0.14	−0.16	0.18	0.27
6. Parental attitudes toward drugs	0.09	0.11	−0.02	−0.26	0.18	1	0.03	0.07	−0.01	0.10	0.01	0.11	−0.17	0.12	0.26
7. Physical or sexual abuse	0.16	0.18	0.01	−0.03	0.02	0.03	1	0.11	0.12	0.01	0.10	0.05	−0.13	0.06	0.11
8. Disruptive behavior 15–17 yrs	0.08	0.33	−0.02	−0.08	0.09	0.07	0.11	1	0.27	0.22	0.16	0.39	−0.28	0.25	0.22
9. Neuroticism	0.11	0.20	0.00	−0.08	0.02	−0.01	0.12	0.27	1	0.04	0.26	0.11	−0.17	0.11	0.04
10. Sensation seeking	0.03	0.16	−0.23	−0.13	0.09	0.11	0.01	0.22	0.04	1	0.03	0.25	−0.19	0.22	0.18
11. Early Onset anxiety disorder	0.12	0.19	−0.05	−0.05	0.03	0.01	0.10	0.16	0.26	0.03	1	0.08	−0.14	0.03	0.11
12. Conduct disorder 15–17 yrs	0.15	0.50	−0.12	−0.16	0.14	0.11	0.05	0.39	0.11	0.25	0.08	1	−0.31	0.47	0.22
13. Parental monitoring	−0.13	−0.33	0.12	0.28	−0.15	−0.16	−0.13	−0.28	−0.17	−0.19	−0.14	−0.31	1	−0.33	−0.24
14. Peer group deviance 15–17 yrs	0.13	0.30	−0.22	−0.23	0.18	0.12	0.06	0.25	0.11	0.22	0.03	0.47	−0.32	1	0.34
15. Cannabis availability	0.18	0.24	−0.34	−0.24	0.11	0.16	0.00	0.19	0.05	0.23	0.05	0.30	−0.30	0.52	1

Correlations between alcohol and cannabis risk factors include the genetic risk of alcohol and cannabis use problems respectively. GR = genetic risk.