Published in final edited form as:
Addict Behav. 2008 February ; 33(2): 235–251. doi:10.1016/j.addbeh.2007.09.002.

Psychiatric and Familial Predictors of Transition Times Between Smoking Stages:

Results From an Offspring-of-Twins Study

Carolyn E. Sartor[a,*], **Hong Xian**[b,c], **Jeffrey F. Scherrer**[a,b], **Michael T. Lynskey**[a], **Alexis E. Duncan**[a], **J. Randolph Haber**[d], **Julia D. Grant**[a], **Kathleen K. Bucholz**[a], and **Theodore Jacob**[d]

a*Department of Psychiatry, Washington University School of Medicine; 660 South Euclid Avenue, Campus Box 8134, St. Louis, MO 63110*

b*Research Service, St. Louis VAMC; 915 North Grand Boulevard, St. Louis, MO 63106*

c*Department of Internal Medicine, Washington University School of Medicine; 660 South Euclid Avenue, Campus Box 8032, St. Louis, MO 63110*

d*Department of Veterans Affairs, Palo Alto Health Care System; 795 Willow Road, MC 151-J, Menlo Park, CA 94025*

Abstract

The modifying effects of psychiatric and familial risk factors on age at smoking initiation, rate of progression from first cigarette to regular smoking, and transition time from regular smoking to nicotine dependence (ND) were examined in 1,269 offspring of male twins from the Vietnam Era Twin Registry. Mean age of the sample was 20.1 years. Cox proportional hazard regression analyses adjusting for paternal alcohol dependence and ND status and maternal ND were conducted. Both early age at first cigarette and rapid transition from initiation to regular smoking were associated with externalizing disorders, alcohol consumption, and cannabis use. Rapid escalation from regular smoking to ND was also predicted by externalizing disorders, but in contrast to earlier transitions, revealed a strong association with internalizing disorders and no significant relationship with use of other substances. Findings characterize a rarely examined aspect of the course of ND development and highlight critical distinctions in risk profiles across stages of tobacco involvement.

Keywords

smoking; stage transition; risk factors; psychopathology; family environment; twin

1. Introduction

The pathway to nicotine dependence (ND) involves a progression through stages of increasingly frequent smoking behaviors and results in an addiction associated with a myriad of negative health outcomes (Fagerstrom, 2002; Bartecchi et al., 1994). Experimental cigarette

*Address correspondence to: Carolyn E. Sartor, Ph.D., Department of Psychiatry, Washington University School of Medicine, 660 South Euclid Ave., Campus Box 8134, St. Louis, MO 63110, USA, Voice: (314) 747-1415, FAX: (314) 286-2213, e-mail: sartorc@psychiatry.wustl.edu

use is developmentally normative among adolescents: over 70% of individuals under the age of 18 have tried at least one cigarette in their lifetimes (CDC, 1998; Nelson and Wittchen, 1998). However, only a subset of experimenters go on to become daily smokers (one-third of those who begin smoking; van den Bree et al., 2004) or to develop ND (approximately half of all daily smokers; Breslau et al., 2001), suggesting that distinct mechanisms may underlie different stages of smoking behaviors. Much of the smoking literature has therefore examined risk factors in relation to the likelihood of reaching particular stages of tobacco involvement (e.g., initiation, regular smoking), but few studies have characterized risk associated with the rate of transition between smoking milestones (e.g., transition time from first cigarette to regular smoking). Given the association of early smoking initiation with increased probability of developing smoking-related problems (Grant, 1998; Hu et al., 2006) and the public health implications of identifying individuals at risk for rapid escalation to greater tobacco involvement, investigation of risk factors that modify the rate of progression between smoking milestones is clearly warranted.

1.1 Psychiatric and familial risk for smoking outcomes

Psychiatric disorders are more prevalent among adult smokers than non-smokers (Black et al., 1999; Farrell et al., 2001; John et al., 2004). The odds of meeting criteria for a psychiatric illness among daily smokers were estimated to be 2.7 times that of non-smokers in one population-based study (Lasser et al., 2000). The link between ND and psychiatric disorders has also been well established: nicotine dependent status is associated with elevated rates of psychiatric illness (Breslau et al., 1994; Grant et al., 2004) and a higher number of comorbid disorders (John et al., 2004). Other substance use disorders (SUDs) are the most consistently identified and robust psychiatric correlates of smoking behaviors (Grant et al., 2004; Upadhyaya et al., 2002), occurring at rates approximately two to three times higher among smokers than non-smokers (Black et al., 1999; Lasser et al., 2000), although mood and anxiety disorders have frequently been associated with smoking behaviors as well (Breslau et al., 1991; Fergusson et al., 2003; Patton et al., 1996).

Investigations of adolescent and young adult cigarette smoking have produced similar findings regarding co-occurring psychopathology: psychiatric disorders, especially SUDs, are more commonly found in smokers (Grucza & Bierut, 2006; Nelson & Wittchen, 1998; Patton et al., 2006; Upadhyaya et al., 2002). Familial and psychiatric risk factors for smoking outcomes have also been examined more broadly in younger samples, revealing risk associated with initiation of alcohol and cannabis use (Dierker et al., 2004; van den Bree et al., 2004) and problem behaviors that originate in childhood (i.e., disruptive disorders, school problems; Dierker et al., 2001; Rohde et al., 2004). Some of these studies have included parenting practices as well (Hill et al., 2005; Lewinsohn et al., 2000), but parental smoking behaviors are the most widely studied. Parental smoking history has been associated with increased likelihood of offspring experimental use, regular smoking, and lifetime ND (Bricker et al., 2007; Flay et al., 1998; Hu et al., 2006). Boomsma and colleagues' work (1994), part of a growing literature on the heritability of smoking behaviors, suggests that the close tie between parental and offspring smoking is attributable to genetic transmission of risk (Boomsma et al., 1994).

Heritability estimates for smoking outcomes span a wide range, from approximately 30% to 80% (Kendler et al., 1999; Maes et al., 2004; True et al., 1997), depending on the sample and phenotype assessed. Much of the genetically-informative research in this area has examined multiple smoking-related constructs in conjunction to determine common and specific liability across phenotypes (Heath et al., 1999; Koopmans et al., 1999; Madden et al., 1999). Cross-phenotype investigations using stages of involvement in tobacco use have provided critical information regarding continuity of genetic contributions over developmental course. For

example, Maes et al. (2004) reported high heritability for initiation of tobacco use, regular smoking, and nicotine dependence (75%, 80%, and 62%, respectively) and substantial genetic correlations between phenotypes, but found that over one-third of genetic liability to ND was attributable to factors specific to ND (Maes et al., 2004). Investigations of common heritable influences on initiation and persistence of smoking (Madden et al., 1999; True et al., 1997) and on initiation and ND (Kendler et al., 1999) have reached a similar conclusion: genetic risk for later stages of smoking behaviors is associated with but not fully explained by heritable contributions to smoking initiation. This line of research has also provided evidence for the substantial role of shared environmental influences on the initiation of cigarette use (accounting for approximately 30% to 55% of the total variance) and the virtual absence of such influences in later stage smoking behaviors (Heath et al., 1999; Madden et al., 1999; Stallings et al., 1999; True et al., 1997). In sum, findings indicate that the relative contributions of environmental versus genetic factors and the nature of heritable influences on smoking behaviors change across stages of tobacco involvement.

1.2 Transitions in the pathway to nicotine dependence

Consistent with genetically-informative research, investigations of psychosocial and psychiatric correlates of smoking milestones have revealed both cross-stage and stage-specific risk factors for progressing to more severe smoking behaviors. Alcohol and cannabis use, especially problem use, have been linked to increased risk for all smoking stage transitions: initiation of smoking (Dierker et al., 2001; Kendler et al., 1999; Rohde et al., 2003), progression from experimental use to regular smoking (Dierker et al., 2004; Rohde et al., 2004), and transition from regular smoking to ND (Breslau et al., 2004; Dierker et al., 2001). Delinquency and externalizing disorders have been tied to progression in smoking behaviors across stages as well (Clark & Cornelius, 2004; Dierker et al., 2004; van den Bree, 2004), whereas evidence that risk conferred by mood and anxiety disorders is global rather than stage-specific is inconsistent (Dierker et al., 2004; Kendler et al., 1999). In contrast, findings regarding the role of familial smoking behaviors (with some exceptions, e.g., Otten et al., 2007) suggest that their impact increases in later smoking stage transitions (Bricker et al., 2007; Dierker et al., 2001; Flay et al., 1998). Taken together, these studies provide a foundation for exploring continuity versus change in psychiatric and familial risk factors for transitions over the course of ND development. The next step is to assess the predictive power of these risk factors for determining the rate of progression to ND across stage transitions.

The current investigation used a genetically-informative design to determine the modifying effects of psychiatric and familial risk factors on transition times at three critical junctures in the pathway to ND. Predictors of the rates of transition from non-use to first cigarette (i.e., age at first cigarette), first cigarette to regular smoking, and regular smoking to ND onset were assessed in a survival analysis format with an offspring-of-twins sample.

2. Method

2.1 Participants

The sample was comprised of 1,269 offspring of twins from the Vietnam Era Twin Registry (VETR), a national registry of male like-sex twin pairs in which both served in the military during the Vietnam Era (1965 - 1975). (Information regarding construction of the VETR and method of determining zygosity has been reported in prior publications [Eisen et al., 1987; Eisen et al., 1989]). Data were drawn from a study of alcohol use disorders (AUDs) and related psychopathology that involved twin pairs, their offspring, and biological mothers of offspring. Selection of twin fathers was based on reports of offspring birth dates collected via questionnaire in 1987 and a structured diagnostic interview conducted in 1992 to obtain fathers' histories of DSM-IIIR drug dependence and other psychiatric diagnoses, including ND and

AD (Tsuang et al., 1996). Male twin pairs were eligible for study participation if one or both members of the pair endorsed full DSM-III-R criteria (lifetime) for AD. A random sample of twin pairs in which neither co-twin was alcohol dependent was also included in this high-risk cohort to serve as a control group. At least one member of each twin pair was required to have one or more offspring born between 1974 and 1988 to be eligible for participation. Response rate for the 1,464 eligible twin fathers was 83% (n = 1,213); 11% declined participation and 6% were deceased, disabled, or could not be located.

Twins were contacted first to obtain permission to contact mothers and offspring. The mothers were then contacted for participation and for permission to contact their children. Participating mothers were associated with 1,588 target offspring. Permission was granted by mothers to contact 1,487 offspring (93.6%), 135 (9%) of whom were unavailable, unlocatable or incapacitated. Of the remaining 1,352 offspring, 1270 (93.9%) were interviewed. Paternal alcohol dependence status was not associated with offspring response rate (Scherrer et al., 2004). One participant was excluded from the present study due to missing age.

Based on father AD status and the AD status of his co-twin, offspring were classified into four AD risk status groups. AD risk group 1 consisted of offspring of alcohol dependent fathers (high genetic (G) and high environmental (E) risk; n=587). AD risk group 2 consisted of offspring of unaffected monozygotic (MZ) twins whose co-twins were positive for AD (high G, low E risk; n=162) and AD risk group 3 consisted of unaffected dizygotic (DZ) twins whose co-twins were positive for AD (moderate G, low E risk; n=157). AD risk group 4 was comprised of offspring of unaffected fathers with unaffected co-twins (low G and low E risk; n=363). In addition to AD risk groups, offspring were categorized into one of four ND risk groups derived from paternal reports of lifetime ND in the 1992 twin assessment. Similar to the AD risk groups, ND risk group 1 (n = 611) was comprised of offspring whose fathers met ND diagnostic criteria (high G, high E); ND risk group 2 (n = 102) consisted of offspring of unaffected MZ twins whose co-twins were positive for ND (high G, low E); ND risk group 3 (n = 139) consisted of offspring of unaffected DZ twins whose co-twins were positive for ND (moderate G, low E); and ND risk group 4 (n = 417) was comprised of offspring whose fathers and fathers' co-twins were unaffected (low G, low E). The rationale for these risk groups has been previously reported (Jacob et al., 2001).

Participants ranged in age from 12 to 28 years, with a mean age of 20.10 years (S.D.=3.98). Female offspring comprised 51.5% of the sample. Approximately 95% of participants self-identified as non-Hispanic Caucasian and 61% of the offspring had fathers who completed 12 or more years of education.

2.2 Procedure

Data were collected from January to November 2001 by the Institute for Survey Research (ISR) at Temple University using Computer Assisted Telephone Interviews (CATI). Interviewers underwent extensive training that involved both ISR staff and project investigators. The Institutional Review Boards at participating institutions approved study protocols prior to the start of data collection. All participants consented to the study prior to the start of interviews.

2.3 Assessment battery

A modified version of the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA-II) (Bucholz et al., 1994; Hesselbrock et al., 1999) was used to collect psychiatric and psychosocial histories from offspring in telephone interviews. Detailed accounts of symptoms and onset of episodes were obtained in addition to lifetime DSM-IV diagnoses for substance use, mood, anxiety, and externalizing disorders. Offspring also reported on

childhood physical and sexual abuse events and on quality of relationships with parents and parental discipline during early childhood (i.e., ages 6-13 years).

Paternal psychiatric diagnoses and demographic information were obtained from histories provided in the 1992 study (Tsuang et al., 1996) in combination with brief telephone interviews conducted at the time of data collection for the current study. Biological mothers were also assessed using an adaptation of the SSAGA-II. Maternal interviews covered mother's history of AUDs and major depression, and included screens for drug use, ND, mania, and antisocial personality disorder. Mother's response to the question "How soon after waking do you smoke your first cigarette?" was used as an index of maternal ND. It is the first question in the Fagerstrom Test for Nicotine Dependence and believed to be the best single indicator of ND (Fagerstrom, 2003). Responses were used as an ordinal variable, with a lower number of minutes to first cigarette indicating increased likelihood of ND (5 or fewer: n = 130; 6-30: n = 139; 31-60: n = 112; 60 or more: n = 148; non-smoker: n = 666). Mothers also provided diagnostic information to assess offspring oppositional defiant disorder (ODD) and attention deficit hyperactivity disorder (ADHD). Approximately 82% of the participating offspring's mothers were interviewed and provided diagnostic data.

2.3.1 Smoking outcomes—Age at first cigarette, age at onset of regular smoking, and age at onset of nicotine dependence were obtained in the history of smoking behaviors provided by offspring in the SSAGA-II. Regular smoking was defined as smoking daily or nearly daily for a period of three weeks or longer. Nicotine dependence referred to full DSM-IV criteria, i.e., 3 or more of the 7 possible ND symptoms reported as occurring in the same 12 month period.

2.3.2 Predictors—Psychiatric and familial correlates of smoking outcomes derived from the literature were assessed as possible predictors of transitions between smoking milestones. Risk factors included parental psychopathology and problem substance use (Brook et al., 2006), history of childhood physical and sexual abuse (Nelson et al., 2006; Nichols & Harlow, 2004), separation from father prior to age 18 (Otten et al., 2007), inconsistent parental discipline and lack of closeness to parents (O'Byrne et al., 2002), female gender (Ridenour et al., 2006), offspring alcohol and cannabis use and use disorders (Dierker et al., 2004; van den Bree et al., 2004), and offspring psychiatric disorders (Nelson & Wittchen, 1998; Upadhyaya et al., 2002). Rates of risk factors in the sample are displayed by domain in Table 1.

2.4 Data Analysis

Three models were constructed to determine the role of psychiatric and familial risk factors in predicting 1) time to first cigarette, 2) time from first cigarette to onset of regular smoking, and 3) time from regular smoking to onset of ND. Given that not all of the offspring had lived through the period of risk for the development of ND, Cox proportional hazards models were chosen to conduct multivariate regression with time-to-event data. Thus, all data was utilized up until the time of censorship (i.e., time of interview) when calculating hazard ratios. Analyses were conducted with STATA, version 8.2 (Statcorp, 2005). Standard deviations of means and confidence intervals for Cox regression models were adjusted for family clustering using Huber-White robust standard errors. The Efron approximation (Hosmer & Lemeshow, 1999) was used to handle ties. With the exception of mother-reported data (i.e., offspring ODD and ADHD diagnoses and maternal psychopathology), complete data were available for nearly all participants (rates of missing data were below 1.5% for variables based on father and offspring reports). Missing data were deleted listwise in Cox regression analyses.

Three dummy variables representing the four AD risk groups (with AD risk group 4 as the common reference group) were included in the models to account for sampling design. Three

dummy variables representing the four ND risk groups (with ND risk group 4 as the common reference group) were also included in the models with the maternal ND variable to adjust for genetic and environmental contributions to smoking outcomes associated with paternal and maternal ND status. Of note, potential covariates included risk factors that varied with regard to age of onset such that onset preceded the age at which a given smoking milestone was reached in some cases but not others (e.g., AD and ND onset). In order to accurately model the contribution of these factors to risk for smoking outcomes, "person year data" was created using SAS, version 9.1 (SAS Institute Inc, 2002) to represent time-varying covariates. Data were constructed with one line of data representing a single year of life for each case. For cases that were positive for a given risk factor, corresponding variables were coded as absent in each year up to the age of onset of the risk factor and present from the year of onset onwards. Time-varying covariates were used for offspring sexual abuse history, substance use disorders, and psychiatric disorders. The assessment of parenting behaviors and physical abuse specifically referenced the period from age 6 to 13 years and parental psychiatric and SUDs were lifetime diagnoses. As a result, parental psychopathology, physical abuse history, and parenting behaviors were time-invariant.

Each of the covariates listed as predictors was tested with maternal ND and the six dummy variables representing paternal AD and ND risk group in two stages. First, covariates were tested by domain (see Table 1). For example, conduct disorder (CD) was tested in combination with the other two offspring externalizing disorders. If the hazard ratios were statistically significant (i.e., confidence intervals did not include 1.00), covariates were retained and then combined with significant covariates from the other domains assessed. The reduced model was derived through manual backward deletion. Covariates that were no longer significant in the context of other predictors were removed one at a time to produce the final model.

To model rate of transition from first cigarette to onset of regular smoking, two dummy variables were created to represent age at first cigarette in order to adjust for variability in proximity of age at first cigarette to the risk period for development of regular smoking. (Chi-square analyses conducted with three levels of age at first cigarette and three levels of transition time to regular smoking were highly significant; $\chi^2 = 77.75$; $p<.001$). The two dummy variables reflected the lowest and highest thirds of the distribution for age at first cigarette, with median age (14-15 years) as the common reference group. "Early age at first cigarette" was defined as initiating smoking at age 13 or younger and "late age at first cigarette" as initiating smoking at age 16 or older. Rate of transition from regular smoking to onset of ND did not differ significantly by age at first cigarette (based on Chi-square analyses conducted with three levels of transition time and three levels of age at first cigarette; $\chi^2 = 8.26$; $p>.05$), so adjustments for age at smoking initiation were not made to the third model.

The proportional hazards assumption that risk remains constant over time was assessed using the Grambsch and Therneau test of the Schoenfeld residuals (Grambsch & Therneau, 1994). The proportional hazard assumption was met for the third model (time from regular smoking to onset of ND) but was violated in the first and second models (time to first cigarette and time from first cigarette to onset of regular smoking). In the first model, maternal ND violated the proportional hazards assumption. To adjust the model, the distribution for years at risk was split into three approximately equal divisions based on frequency: 0-13, 14-15, and 16 or more years, and interaction terms were created between each of the three divisions with maternal ND status. Interaction terms were entered into the model one at a time to test for changes in the proportional hazard estimations. The addition of the interaction term representing maternal ND by the risk period from 14-15 years of age resolved the violation of the proportional hazard assumption. The same procedure was followed to adjust proportional hazard violations for alcohol use and early age at first cigarette in the second model. The distribution of years at risk from first cigarette to onset of regular smoking was split by frequency into three divisions: 0-1,

2-3, and 4 or more years and interaction terms created with the two covariates. Violations were corrected by including interaction terms representing early age at first cigarette with the 0-1 year risk period and early age at first cigarette with the 2-3 year risk period in the model.

3. Results

3.1 Smoking milestones and transition times

The majority of participants had smoked one or more cigarettes during their lifetimes (64.5%; n = 817), 26.2% (n = 332) of the total sample progressed to regular smoking, and 9.6% (n = 122) met lifetime criteria for ND. First cigarette was smoked on average at 14.17 (S.D. = 2.96) years of age, regular smoking began at a mean age of 16.62 (S.D. = 2.31) years, and mean onset of ND occurred at 18.40 (S.D. = 2.69) years of age. Rate of transition from first cigarette to regular smoking ranged from 0 to 11 years, with approximately half of regular smokers reporting 2 or fewer years from first cigarette to the onset of regular smoking. Transition times from regular smoking to ND onset covered a comparable range (0 to 10 years), but greater than two thirds reported 2 or fewer years from the start of regular smoking to the development of ND.

3.2 Predictors of age at first cigarette

Results from the Cox proportional hazards regression model predicting age at first cigarette are shown in Table 2. After adjusting for risk conferred by paternal ND and AD status and maternal ND, offspring use of other substances predicted age at initiation of smoking. Cannabis and alcohol use were associated with nearly two and a half fold increases in the rate of onset for cigarette smoking. ODD (HR: 1.69) and maternal AD (HR: 1.37) also predicted early age at first cigarette, as did both maternal ND (HR: 1.08) and paternal ND (ND risk group 1) (HR: 1.22). The interaction term representing maternal ND by the risk period 14-15 years of age, included in the model to adjust for proportional hazards violations, was associated with a slower rate of onset for first cigarette (HR: 0.88), indicating that the influence of maternal ND on smoking initiation was diminished during that portion of the risk period.

3.3 Predictors of transition time from first cigarette to regular smoking

In the second regression model, which estimated rate of progression from first cigarette to regular smoking, other substance use and externalizing problems were also associated with an elevated rate of transition, even after adjusting for age at first cigarette, paternal ND and AD status, and maternal ND (see Table 3). Cannabis use (HR: 2.38) was the most potent predictor of a rapid transition from first cigarette to regular smoking, followed by CD (HR: 1.64) and alcohol use (HR: 1.56). Paternal ND was associated with an increased rate of transition as well (HR: 1.66). The two interaction terms added to the model to adjust for violations of the proportional hazard assumption, which represented early age at first cigarette by the risk periods up to 1 year and 2-3 years after first cigarette, predicted increased rate of progression to regular smoking (HR: 2.68 and 6.51, respectively). That is, the effects of early first cigarette on rapid transition to regular smoking were most pronounced in the first 3 years after smoking initiation.

3.4 Predictors of transition time from regular smoking to onset of ND

Results of the regression model predicting rate of progression from regular smoking to onset of ND are summarized in Table 4. Consistent with the models depicting initiation of cigarette smoking and transition to regular smoking, externalizing disorders were associated with elevated risk for a rapid transition from regular smoking to onset of ND. Hazard ratios were 3.62 and 2.32 for CD and ODD, respectively, but it was the internalizing disorders that demonstrated the largest effects. The most robust predictor of rapid escalation to ND was panic

disorder, with a hazard ratio of 13.28. Greater than four-fold increases in rate of progression from regular smoking to ND were also found for both major depressive disorder and social phobia.

4. Discussion

In the current study, psychiatric and familial risk factors for escalation in smoking behaviors were examined across three stage transitions using an offspring-of-twins design, thus extending the current literature in two ways. First, the adjustments for maternal ND and for paternal ND and AD risk conferred by genetic and environmental exposures provided a robust test for the association of psychiatric disorders and the family environment with transitioning to greater tobacco involvement. Second, by characterizing risk for rapid movement between stages the current investigation captured an aspect of developmental course that is not addressed when simply predicting whether a stage of ND development is ever reached.

The examination of three key transition points in the development of ND provided the opportunity to address continuity versus specificity of psychiatric and familial risk across stage transitions in the progression to greater tobacco involvement. Similar to investigations examining predictors of reaching a given smoking milestone, findings from the current study indicated that certain risk factors are associated with speed of transitions across multiple stages of development of the disorder, whereas others impact the rate of escalation only during specific stages.

4.1 Cross-stage predictors of transitions

Results produced evidence of continuity in risk conferred by externalizing disorders for rapid transitions across the three smoking stages: ODD predicted early initiation, CD was associated with escalation to regular smoking, and both had significant effects on the transition to ND. Childhood antisocial behavior has been linked to early experimentation with cigarettes in numerous previous investigations (Clark & Cornelius, 2004; Dierker et al., 2001; Rohde et al., 2004; van den Bree et al., 2004) and elevated rates of regular smoking and ND among individuals with externalizing psychopathology are well documented (Disney et al., 1999; Galera et al., 2004; Kollins et al., 2005; Tercyak et al., 2002). The current findings suggest that externalizing disorders impact yet another dimension of ND development: the *rate* of progression between smoking stages. Furthermore, as the study design included control for genetic factors associated with ND and AD, our results indicate that this association is not fully accounted for by genetic risk shared with these disorders.

Consistent with previous studies demonstrating an association between alcohol consumption and early age at first cigarette (Grant, 1998; Rohde et al., 2003), earlier onset of smoking initiation was predicted by alcohol use, as was rapid transition to regular smoking. Although rarely investigated in relation to the rate of progression across stages of tobacco involvement, there is a large literature tying alcohol use to smoking (Grucza & Bierut, 2006; Dierker et al., 2004; Koopmans et al., 1997; Weitzman & Chen, 2005) that includes evidence of comorbid alcohol use and smoking trajectories spanning young adulthood (Jackson et al., 2005). Shared heritability (adjusted for in the current investigation) is among the best documented risk factors (Bierut et al., 2004; Connor et al., 2007; True et al., 1999; Young et al., 2006). Thus, though the link between alcohol use and smoking is predictable, the robustness of these findings is noteworthy. Associations were found in analyses that accounted for maternal ND in addition to paternal genetic and environmental contributions to AD and ND and used time-varying covariates to model order of onset for smoking and alcohol use behaviors.

Cannabis use produced a similar pattern of results. It was associated with earlier age at first cigarette and rapid transition from first cigarette to regular smoking. Findings were consistent

with the increased probability of experimentation with cannabis found in smokers (Ellickson et al., 2004a; Faeh et al., 2006) and the high rates of smoking among cannabis users (Degenhardt et al., 2001; Swift et al., 2001; Reid et al., 2000), but added to this literature by portraying the role of cannabis use in escalating tobacco involvement. Although suggestive of an atypical sequence of substance involvement, with tobacco use generally believed to precede initiation of cannabis use (Kandel, 1975; Kandel et al., 1992), findings are compatible with a growing literature demonstrating that the sequence of substance use is not universal (Amos et al., 2004; Guerra et al., 2000; Wetzels et al., 2003). Our results parallel recent evidence that cannabis use predicts both smoking initiation and progression to ND (Patton et al., 2005; Timberlake et al., 2006).

The absence of significant findings for alcohol and cannabis use (or alcohol/cannabis use disorders) on the rate of transition from regular smoking to ND merits comment as well. Rather than indicating that they are unrelated to the rate of escalation to ND, the lack of effects may reflect the absence of unique variance accounted for by alcohol and cannabis use - independent of the variance accounted for by genetic risk for ND and AD. An increase from early to later stage transitions in the overlap of variance in genetic risk for ND and AD with variance in alcohol and cannabis use would also explain this finding. Evidence for changes in the source of genetic contributions to smoking outcomes across stages (i.e., heritability of smoking initiation is not perfectly correlated with heritability for progression to heavier use [Fowler et al., 2006] or ND [Kendler et al., 1999; Maes et al., 2004]) lends support to this interpretation of the results.

4.2 Stage-specific predictors of transitions

Maternal AD predicted early smoking initiation, but was not associated with the speed of later stage transitions, paralleling findings from an earlier investigation of alcohol stage transitions conducted by our group (Sartor et al., 2007). The emergence in the final stage transition of internalizing disorders as accelerators of the shift from regular smoking to ND, by contrast, has rarely been reported and is best interpreted in the context of the larger literature on mood and anxiety disorders as they relate to smoking behaviors.

Elevated rates of regular smoking and ND have been found for individuals with affective and anxiety disorders in a number of studies (Breslau et al., 1991; Fergusson et al., 2003; John et al, 2004; Patton et al., 1996), but some reports have indicated that the association disappears when examined in the context of additional psychiatric and SUDs (Black et al., 1999; Grant et al., 2004; Rohde et al., 2004). Investigations involving multiple stages of tobacco involvement suggest that inconsistencies across studies may be attributable in part to differences in the operationalization of the smoking phenotypes examined. In a longitudinal study spanning adolescence to young adulthood for example, social phobia was associated with increased likelihood of transitioning from regular smoking to ND but not of progressing to regular smoking (Sonntag et al., 2000). Persistent depression and anxiety similarly predicted progression to ND but not onset of daily smoking in an Australian sample followed for 10 years (Patton et al., 2006). A large, population-based study in Germany also revealed clear distinctions in the role of internalizing disorders for initiation of smoking versus the transition to dependent smoking status. Across mood and anxiety disorders, effects were non-significant for the earlier stage transition and significant for the transition from regular smoking to ND (Schumann et al., 2004). The convergence of findings is striking and suggestive of a later stage specificity in the impact of internalizing disorders on progressive tobacco involvement, but given the limited literature in this area, conclusions are best viewed as preliminary. Moreover, the approach used in the current study is distinct from that used in prior literature in its characterization of the speed of progression through stages, making direct comparisons to previous findings difficult. A complete account of mechanisms underlying the stage transitions

described in our results is beyond the scope of this study, but the integration of these findings into an etiological model of the development of the disorder and an exploration of their clinical implications are clearly warranted.

4.3 Clinical implications

The findings from the current study portray a three-stage pathway from smoking initiation to the onset of ND. The beginning of the pathway, in which externalizing behaviors and other substance use are tied to early smoking initiation and a rapid movement to regular smoking, is frequently described in the literature as a problem behavior syndrome (Donovan & Jessor, 1985; Jessor & Jessor, 1977) that is perpetuated by environmental exposures and responses to antisocial behaviors, e.g., association with deviant peers (Ary et al., 1999; Dishion et al., 2004; Dodge & Pettit, 2003). By contrast, the prominent role of internalizing disorders in combination with the continued influence of externalizing disorders on escalation from regular smoking to ND suggests that the mechanisms underlying this later stage transition differ from (or are more diverse than) those that contribute to the early stages of tobacco involvement. The clinical implications of these findings are two-fold. First, the pathway of progressive tobacco involvement is determined by modifiable risk factors in addition to genetics. The risk factors described in our results were identified after stringently controlling for paternal and maternal genetic contributions to ND (as well as paternally transmitted genetic risk for AD). Furthermore, the distinctions in risk profiles across stage transitions underscore the importance of ongoing assessment and treatment of comorbid disorders that shape the developmental course of tobacco involvement. Those individuals at risk for progression early on in the course of ND development (e.g., behaviorally undercontrolled adolescents who drink and use cannabis) may not be the same as those who move rapidly from regular smoking to ND (e.g., anxiety-prone or depressed youth).

4.4 Limitations and future directions

The current study has some limitations, which suggest possible directions for future research in this area. First, as the sample is relatively well-educated and largely Caucasian, replication with more diverse samples would be needed to determine whether variability by socioeconomic status (Jerfferis et al., 2003; Tyas et al., 1998) and ethnicity (Blitstein et al., 2003; Ellickson et al., 2004b) in smoking outcomes extend to distinctions in psychiatric and familial risk factors for rate of stage transitions. Second, although bias was minimized through the use of survival analytic strategies, the sample included adolescents not yet through the age of risk for ND, so findings may more accurately characterize smoking transitions among early onset cases of ND. Third, smoking histories were reported retrospectively, and though covering a relative short period of time, prospective assessments would likely produce more reliable accounts. Fourth, a broad range of psychiatric risk factors encompassing the most common forms of psychopathology were examined, but not every disorder associated with smoking behaviors was assessed (e.g., psychotic disorders, Hughes et al., 1986; McCreadie et al., 2002). Fifth, findings suggest that treating co-morbid disorders may have an impact the course of ND development, but direct tests of this hypothesis have yet to be conducted. Finally, the present investigation was focused on familial and psychiatric correlates of smoking stage transitions and did not address friends' or siblings' influences on smoking. The integration in future studies of stage-specific peer smoking behaviors would create the opportunity to explore the interaction of peer and environmental selection with genetic risk for ND in the progression of smoking behaviors.

Acknowledgements

This study was funded by grants AA11667, AA11822, AA007580, and AA11998 from the National Institute on Alcohol Abuse and Alcoholism, grants DA18660, DA14363, and DA18267 from the National Institute on Drug Abuse,

and from a Merit Review Grant (Jacob) from the Department of Veterans Affairs Medical Research Service. The Department of Veterans Affairs has provided financial support for the development and maintenance of the VET Registry. Numerous organizations have provided invaluable assistance in the conduct of this study, including: Department of Defense, National Personnel Records Center, National Archives and Records Administration, the Internal Revenue Service, National Opinion Research Center, National Research Council, National Academy of Sciences, and the Institute for Survey Research at Temple University. Most importantly, the authors gratefully acknowledge the continued cooperation and participation of the members of the VET Registry and their families.

References

Amos A, Wiltshire S, Bostock Y, Haw S, McNeill A. 'You can't go without a fag... you need it for your hash' - a qualitative exploration of smoking, cannabis, and young people. Addiction 2004;99:77–81. [PubMed: 14678065]

Bartecchi CE, MacKenzie TD, Schrier RW. The human costs of tobacco use - First of two parts. The New England Journal of Medicine 1994;330:907–912. [PubMed: 8114863]

Bierut LJ, Rice JP, Goate A, Hinrichs AL, Saccone NL, Foroud T, et al. A genomic scan for habitual smoking in families of alcoholics: Common and specific genetic factors in substance dependence. American Journal of Medical Genetics 2004;124:19–27. [PubMed: 14679582]

Black DW, Zimmerman M, Coryell WH. Cigarette smoking and psychiatric disorder in a community sample. Annals of Clinical Psychiatry 1999;11:129–136. [PubMed: 10482122]

Blitstein JL, Robinson LA, Murray DM, Klesges RC, Zbikowski SM. Rapid progression to regular cigarette smoking among nonsmoking adolescents: interactions with gender and ethnicity. Preventive Medicine 2003;36:455–463. [PubMed: 12649054]

Boomsma DI, Koopmans JR, Van Dooren LJP, Orlebeke JF. Genetic and social influences on starting to smoke: a study of Dutch adolescent twins and their parents. Addiction 1994;89:219–226. [PubMed: 8173488]

Breslau N, Johnson EO, Hiripi E, Kessler R. Nicotine dependence in the United States: prevalence, trends, and smoking persistence. Archives of General Psychiatry 2001;58:810–816. [PubMed: 11545662]

Breslau N, Kilbey M, Andreski P. Nicotine dependence, major depression, and anxiety in young adults. Archives of General Psychiatry 1991;48:1069–1074. [PubMed: 1845224]

Breslau N, Kilbey MM, Andreski P. DSM-III-R nicotine dependence in young adults: prevalence, correlates, and associated psychiatric disorders. Addiction 1994;89:743–754. [PubMed: 8069175]

Breslau N, Novak SP, Kessler RC. Psychiatric disorders and stages of smoking. Biological Psychiatry 2004;55:69–76. [PubMed: 14706427]

Bricker JB, Peterson AV Jr. Sarason IG, Anderson MR, Rajan KB. Changes in the influence of parents' and close friends' smoking on adolescent smoking transitions. Addictive Behaviors 2007;32:740–757. [PubMed: 16854532]

Brook DW, Brook JS, Rubenstone E, Zhang C, Gerochi C. Pediatrics 2006;117:1339–1347. [PubMed: 16585332]

Bucholz KK, Cadoret R, Cloninger CR, Dinwiddie SH, Hesselbrock VM, Nurnberger JI, et al. A new, semi-structured psychiatric interview for use in genetic linkage studies: A report of the reliability of the SSAGA. Journal of Studies on Alcohol 1994;55:149–58. [PubMed: 8189735]

Centers for Disease Control and Prevention (CDC). Selected cigarette smoking initiation and quitting behaviors among high school students--United States, 1997. MMWR. Morbidity and Mortality Weekly Report 1998;47:386–389. [PubMed: 9614006]

Clark DB, Cornelius J. Childhood psychopathology and adolescent cigarette smoking: A prospective survival analysis in children at high risk for substance use disorders. Addictive Behaviors 2004;29:837–841. [PubMed: 15135569]

Connor JP, Young R. McD. Lawford BR, Saunders JB, Ritchie TL, Noble EP. Heavy nicotine and alcohol use in alcohol dependence is associated with D2 dopamine receptor (DRD2) polymorphism. Addictive Behaviors 2007;32:310–319. [PubMed: 16766132]

Degenhardt L, Hall W, Lynskey M. The relationship between cannabis use and other substance use in the general population. Drug and Alcohol Dependence 2001;64:319–327. [PubMed: 11672946]

Dierker LC, Avenevoli S, Goldberg A, Glantz M. Defining subgroups of adolescents at risk for experimental and regular smoking. Prevention Science 2004;5:169–183. [PubMed: 15470937]

Dishion TJ, Nelson SE, Winter CE, Bullock BM. Adolescent friendship as a dynamic system: Entropy and deviance in the etiology and course of male antisocial behavior. Journal of Abnormal Child Psychology 2004;32:651–663. [PubMed: 15648531]

Dierker LC, Avenevoli S, Merikangas KR, Flaherty BP, Stolar M. Association between psychiatric disorders and the progression of tobacco use behaviors. Journal of the American Academy of Child and Adolescent Psychiatry 2001;40:1159–1167. [PubMed: 11589528]

Disney ER, Elkins IJ, McGue M, Iacono WG. Effects of ADHD, conduct disorder, and gender on substance use and abuse in adolescence. American Journal of Psychiatry 1999;156:1515–1521. [PubMed: 10518160]

Dodge KA, Pettit GS. A biopsychosocial model of the development of chronic conduct problems in adolescence. Developmental Psychology 2003;39:349–371. [PubMed: 12661890]

Donovan JE, Jessor R. Structure of problem behavior in adolescence and young adulthood. Journal of Consulting and Clinical Psychology 1985;53:890–904. [PubMed: 4086689]

Eisen S, Neuman R, Goldberg J, Rice J, True W. Determining zygosity in the Vietnam Era Twin Registry: an approach using questionnaires. Clinical Genetics 1989;35:423–432. [PubMed: 2736790]

Eisen S, True W, Goldberg J, Henderson W, Robinette CD. The Vietnam Era Twin (VET) Registry: Method of construction. Acta Geneticae Medicae et Gemellologiae 1987;36:61–67. [PubMed: 3673478]

Ellickson PL, Orlando M, Tucker JS, Klein DJ. From adolescence to young adulthood: racial/ethnic disparities in smoking. Research and Practice 2004;94:293–299.

Ellickson PL, Tucker JS, Klein DJ, Saner H. Antecedents and outcomes of marijuana use initiation during adolescence. Preventive Medicine 2004;39:976–984. [PubMed: 15475032]

Fagerstrom K. The epidemiology of smoking. Health consequences and benefits of cessation. Drugs 2002;62(Suppl 2):1–9. [PubMed: 12109931]

Fagerstrom K. Time to first cigarette; the best single indicator of tobacco dependence? Monaldi Archives for Chest Disease 2003;59:91–94. [PubMed: 14533289]

Faeh D, Viswanathan B, Chiolero A, Warren W, Bovet P. BMC Public Health 2006;6:169–176. [PubMed: 16803621]

Farrell M, Howes S, Bebbington P, Brugha T, Jenkins R, Lewis G, et al. Nicotine, alcohol, and drug dependence and psychiatric comorbidity - results of a national household survey. British Journal of Psychiatry 2001;179:432–437. [PubMed: 11689401]

Fergusson DM, Goodwin RD, Horwood LJ. Major depression and cigarette smoking: results of a 21-year longitudinal study. Psychological Medicine 2003;33:1357–1367. [PubMed: 14672244]

Flay BR, Hu FB, Richardson J. Psychosocial predictors of different stages of cigarette smoking among high school students. Preventive Medicine 1998;27:A9–A18. [PubMed: 9808813]

Fowler T, Lifford K, Shelton K, Rice F, Thapar A, Neale M, et al. Exploring the relationship between genetic and environmental influences on initiation and progression of substance use. Addiction 2006;101:413–422. [PubMed: 16499514]

Galera C, Fombonne E, Chastang J-F, Bouvard M. Childhood hyperactivity-inattention symptoms and smoking in adolescence. Drug and Alcohol Dependence 2004;78:101–108. [PubMed: 15769563]

Grambsch P, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 1994;81:515–526.

Grant B. Age at smoking onset and its association with alcohol consumption and DSM-IV alcohol abuse and dependence: Results from the National Longitudinal Alcohol Epidemiologic Survey. Journal of Substance Abuse 1998;10:59–73. [PubMed: 9720007]

Grant BF, Hasin DS, Chou P, Stinson FS, Dawson DA. Nicotine dependence and psychiatric disorders in the United States. Archives of General Psychiatry 2004;61:1107–1115. [PubMed: 15520358]

Grucza RA, Bierut LJ. Cigarette smoking and the risk for alcohol use disorders among adolescent drinkers. Alcoholism: Clinical and Experimental Research 2006;30:2046–2054.

Guerra LM, Romano PS, Samuels SJ, Kass PH. Ethnic differences in adolescent substance initiation sequences. Archives of Adolescent and Pediatric Medicine 2000;154:1089–1095.

Heath AC, Kirk KM, Meyer JM, Martin NG. Genetic and social determinants of initiation and age at onset of smoking in Australian twins. Behavior Genetics 1999;29:395–407. [PubMed: 10857245]

Hesselbrock M, Easton C, Bucholz KK, Schuckit M, Hesselbrock V. A validity study of the SSAGA - A comparison with the SCAN. Addiction 1999;94:1361–1370. [PubMed: 10615721]

Hill KG, Hawkins JD, Catalano RF, Abbott RD, Guo J. Family influences on the risk of daily smoking. Journal of Adolescent Health 2005;37:202–210. [PubMed: 16109339]

Hosmer, DW.; Lemeshow, S. Applied survival analysis: Regression modeling of time to event data. John Wiley & Sons; New York: 1999.

Hu M-C, Davies M, Kandel D. Epidemiology and correlates of daily smoking and nicotine dependence among young adults in the United States. Research and Practice 2006;96:299–308.

Hughes JR, Hatsukami DK, Mitchell JE, Dahlgren LA. Prevalence of smoking among psychiatric outpatients. American Journal of Psychiatry 1986;143:993–997. [PubMed: 3487983]

Jackson KM, Sher KJ, Schulenberg JE. Conjoint developmental trajectories of young adult alcohol and tobacco use. Journal of Abnormal Psychology 2005;114:612–626. [PubMed: 16351384]

Jacob T, Sher KJ, Bucholz KK, True WT, Sirevaag EJ, Rohrbaugh J, et al. An integrative approach for studying the etiology of alcoholism and other addictions. Twin Research 2001;4:103–118. [PubMed: 11665331]

Jefferis B, Graham H, Manor O, Power C. Cigarette consumption and socioeconomic circumstances in adolescence as predictors of adult smoking. Addiction 2003;98:1765–1772. [PubMed: 14651509]

Jessor, R.; Jessor, SL. Problem behavior and psychosocial development: A longitudinal study of youth. Academic Press; New York: 1977.

John U, Meyer C, Rumpf H-J, Hapke U. Smoking, nicotine dependence and psychiatric comorbidity - a population-based study including smoking cessation after three years. Drug and Alcohol Dependence 2004;76:287–295. [PubMed: 15561479]

Kandel DB. Stages in adolescent involvement in drug use. Science 1975;190:912–914. [PubMed: 1188374]

Kandel DB, Yamaguchi K, Chen K. Stages of progression in drug involvement from adolescence to adulthood: further evidence for the gateway theory. Journal of Studies on Alcohol 1992;53:447–457. [PubMed: 1405637]

Kendler KS, Neale MC, Sullivan P, Corey LA, Gardner CO, Prescott CA. A population-based twin study in women of smoking initiation and nicotine dependence. Psychological Medicine 1999;29:299–308. [PubMed: 10218922]

Kollins SH, McClernon J, Fuemmeler BF. Association between smoking and attention-deficit/hyperactivity disorder symptoms in a population-based sample of young adults. Archives of General Psychiatry 2005;62:1142–1147. [PubMed: 16203959]

Koopmans JR, Slutske WS, Heath AC, Neale MC, Boomsma DI. The genetics of smoking initiation and quantity smoked in Dutch adolescent and young adult twins. Behavior Genetics 1999;29:383–393. [PubMed: 10857244]

Koopmans JR, van Doornen JP, Boomsma DI. Association between alcohol use and smoking in adolescent and young adult twins: A bivariate genetic analysis. Alcoholism: Clinical and Experimental Research 1997;21:537–546.

Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: A population-based prevalence study. Journal of the American Medical Association 2000;284:2606–2610. [PubMed: 11086367]

Lewinsohn PM, Brown RA, Seeley JR, Ramset SE. Psychosocial correlates of cigarette smoking abstinence, experimentation, persistence, and frequency during adolescence. Nicotine and Tobacco Research 2000;2:121–131. [PubMed: 11072450]

Madden PAF, Heath AC, Pedersen NL, Kaprio J, Koskenvuo MJ, Martin NG. The genetics of smoking persistence in men and women: A multicultural study. Behavior Genetics 1999;29:423–431. [PubMed: 10857247]

Maes HH, Sullivan PF, Bulik CM, Neale MC, Prescott CA, Eaves LJ, et al. A twin study of genetic and environmental influences on tobacco initiation, regular tobacco use and nicotine dependence. Psychological Medicine 2004;34:1251–1261. [PubMed: 15697051]

McCreadie RG. Use of drugs, alcohol, and tobacco by people with schizophrenia: case-control study. British Journal of Psychiatry 2002;181:321–325. [PubMed: 12356659]

Nelson CB, Wittchen H-U. Smoking and nicotine dependence. Results from a sample of 14-24 year-olds in Germany. European Addiction Research 1998;4:42–49. [PubMed: 9740816]

Nelson EC, Heath AC, Lynskey MT, Bucholz KK, Madden PAF, Statham DJ, et al. Childhood sexual abuse and risks for licit and illicit drug-related outcomes: a twin study. Psychological Medicine 2006;36:1473–1483. [PubMed: 16854248]

Nichols HB, Harlow BL. Childhood abuse and risk of smoking onset. Journal of Epidemiology and Community Health 2004;58:402–406. [PubMed: 15082739]

O'Byrne KK, Haddock CK, Poston WSC. Parenting style and adolescent smoking. Journal of Adolescent Health 2002;30:418–425. [PubMed: 12039511]

Otten R, Engels RCME, van de Ven MOM, Bricker JB. Parental smoking and adolescent smoking stages: the role of parents' current and former smoking, and family structure. Journal of Behavioral Medicine 2007;30:143–154. [PubMed: 17221319]

Patton GC, Coffey C, Carlin JB, Sawyer SM, Lynskey M. Reverse gateways? Frequent cannabis use as a predictor of tobacco initiation and nicotine dependence. Addiction 2005;100:1518–1525. [PubMed: 16185213]

Patton GC, Coffey C, Carlin JB, Sawyer SM, Wakefield M. Teen smokers reach their mid twenties. Journal of Adolescent Health 2006;39:214–220. [PubMed: 16857533]

Patton GC, Hibbert M, Rosier MJ, Carlin JB, Caust J, Bowes G. Is smoking associated with depression and anxiety in teenagers? American Journal of Public Health 1996;86:225–230. [PubMed: 8633740]

Reid A, Lynskey M, Copeland J. Cannabis use among Australian adolescents: findings of the 1998 National Drug Strategy Household Survey. Australian and New Zealand Journal of Public Health 2000;24:596–602. [PubMed: 11215007]

Ridenour TA, Lanza ST, Donny EC, Clark DB. Different lengths of times for progressions in adolescent substance involvement. Addictive Behaviors 2006;31:962–983. [PubMed: 16677774]

Rohde P, Kahler CW, Lewinsohn PM, Brown RA. Psychiatric disorders, familial factors, and cigarette smoking: II. Associations with progression to daily smoking. Nicotine and Tobacco Research 2004;6:119–132. [PubMed: 14982696]

Rohde P, Lewinsohn PM, Brown RA, Gau JM, Kahler CW. Psychiatric disorders, familial factors, and cigarette smoking: I. Associations with smoking initiation. Nicotine and Tobacco Research 2003;5:85–98. [PubMed: 12745510]

Sartor CE, Lynskey MT, Heath AC, Jacob T, True W. The role of childhood risk factors in initiation of alcohol use and progression to alcohol dependence. Addiction 2007;102:216–225. [PubMed: 17222275]

SAS Institute Inc.; Cary, NC: 2002.

Scherrer JF, Waterman BM, Heath AC, Bucholz KK, True WR, Jacob T. Are substance use, abuse and dependence associated with study participation? Predictors of offspring nonparticipation in a twin-family study. Journal of Studies on Alcohol 2004;65:140–44. [PubMed: 15000514]

Schumann A, Hapke U, Meyer C, Rumpf H-J, John U. Prevalence, characteristics, associated mental disorders, and predictors of DSM-IV nicotine dependence. European Addiction Research 2004;10:29–34. [PubMed: 14665803]

Sonntag H, Wittchen HU, Hofler M, Kessler RC, Stein MB. Are social fears and DSM-IV social anxiety disorder associated with smoking and nicotine dependence in adolescents and young adults? European Psychiatry 2000;15:67–74. [PubMed: 10713804]

Stallings MC, Hewitt JK, Beresford T, Heath AC, Eaves LJ. A twin study of drinking and smoking onset and latencies from first use to regular use. Behavior Genetics 1999;29:409–421. [PubMed: 10857246]

Statacorp. Stata Statistical Software: Release 8.2. College Station, TX: 2005.

Swift W, Hall W, Teesson M. Cannabis use and dependence among Australian adults: results from the National Survey of Mental Health and Wellbeing. Addiction 2001;96:737–748. [PubMed: 11331032]

Tercyak KP, Lerman C, Audrain J. Association of attention-deficit/hyperactivity disorder symptoms with levels of cigarette smoking in a community sample of adolescents. Journal of the American Academy of Child and Adolescent Psychiatry 2002;41:799–805. [PubMed: 12108804]

Timberlake DS, Haberstick BC, Hopfer CJ, Bricker J, Sakai JT, Lessem JM, et al. Progression from marijuana use to daily smoking and nicotine dependence in a national sample of U.S. adolescents. Drug and Alcohol Dependence. in press

True WR, Heath AC, Scherrer JF, Waterman B, Goldberg J, Lin N, et al. Genetic and environmental contributions to smoking. Addiction 1997;92:1277–1287. [PubMed: 9489045]

True WR, Xian H, Scherrer JF, Madden PAF, Bucholz KK, Heath AC, et al. Common genetic vulnerability for nicotine dependence and alcohol dependence in men. Archives of General Psychiatry 1999;56:655–661. [PubMed: 10401514]

Tsuang MT, Lyons MJ, Eisen S, Goldberg J, True W, Meyer J, et al. Genetic influences on DSM-III-R drug abuse and dependence: a study of 3,372 twin pairs. American Journal of Medical Genetics 1996;67:373–77.

Tyas SL, Pederson LL. Psychosocial factors related to adolescent smoking: a critical review of the literature. Tobacco Control 1998;7:409–420. [PubMed: 10093176]

Upadhyaya HP, Deas D, Brady KT, Kruesi M. Cigarette smoking and psychiatric comorbidity in children and adolescents. Journal of the American Academy of Child and Adolescent Psychiatry 2002;41:1294–1305. [PubMed: 12410071]

van den Bree MBM, Whitmer MD, Pickworth WB. Predictors of smoking development in a population-based sample of adolescents: A prospective study. Journal of Adolescent Health 2004;35:172–181. [PubMed: 15313498]

Weitzman ER, Chen Y-Y. The co-occurrence of smoking and drinking among young adults in college: National survey results from the United States. Drug and Alcohol Dependence 2005;80:377–386. [PubMed: 16009507]

Wetzels JJL, Kremers SPJ, Vitoria PD, de Vries H. The alcohol-tobacco relationship: a prospective study among adolescents in six European countries. Addiction 2003;98:1755–1763. [PubMed: 14651508]

Young SE, Rhee SH, Stallings MC, Corley RP, Hewitt JK. Genetic and environmental vulnerabilities underlying adolescent substance use and problem use: General or specific? Behavior Genetics 2006;36:603–615. [PubMed: 16619135]

Table 1

Prevalence of Risk Factors

Familial Psychiatric History, Family Environment, and Gender

Parental Psychiatric History (Lifetime)	
Paternal antisocial personality disorder	2.8%
Paternal major depressive disorder	8.2%
Paternal drug dependence	11.9%
Maternal alcohol dependence	9.5%
Maternal major depressive disorder	17.7%
Parenting (Offspring Report For Ages 6-13)	
Not close to father	10.7%
Not close to mother	4.8%
Father inconsistent with discipline	11.8%
Mother inconsistent with discipline	12.0%
Offspring Abuse History	
Physical abuse (ages 6-13)	4.1%
Sexual abuse	6.7%
Gender: female	51.5%

Offspring Substance Use and Psychiatric Disorders

Substance Use and Abuse/Dependence	
Alcohol use	79.4%
Alcohol dependence	10.0%
Cannabis use	46.2%
Cannabis abuse	8.7%
Externalizing Disorders	
Attention deficit hyperactivity disorder	6.2%
Conduct disorder	5.8%
Oppositional defiant disorder	6.2%
Internalizing Disorders	
Major depressive disorder	14.5%
Generalized anxiety disorder	2.5%
Panic disorder	2.1%
Social phobia	8.9%

Table 2

Cox proportional hazards model for time to first cigarette (n = 1,269)

	Hazard Ratio (95% CI)
Cannabis use*	2.50 (1.99 - 3.15)
Alcohol use*	2.42 (1.99 - 2.94)
Oppositional defiant disorder*	1.69 (1.34 - 2.13)
Maternal alcohol dependence*	1.37 (1.10 - 1.70)
Nicotine dependence risk group (based on paternal status)[a]	
Group 1: high genetic (G), high environmental (E)*	1.22 (1.01 - 1.49)
Group 2: high G, low E	1.14 (0.80 - 1.62)
Group 3: moderate G, low E	1.05 (0.79 - 1.40)
Alcohol dependence risk group (based on paternal status)[a]	
Group 1: high G, high E	1.07 (0.87 - 1.33)
Group 2: high G, low E	1.12 (0.86 - 1.47)
Group 3: moderate G, low E	1.03 (0.79 - 1.35)
Maternal nicotine dependence (Fagerstrom proxy)	1.08 (1.02 - 1.16)
Maternal ND X risk period from 14-15 years of age [b]*	0.88 (0.79 - 0.98)

[a] Hazard ratios relative to Group 4 (control)

[b] Interaction term included in the model to adjust for violation of proportional hazard assumption for maternal nicotine dependence.

* $p < .05$

Table 3

Cox proportional hazards model for transition time from first cigarette to onset of regular smoking (n = 817)

	Hazard Ratio (95% CI)
Cannabis use*	2.38 (1.83 - 3.11)
Conduct disorder*	1.64 (1.15 - 2.34)
Alcohol use*	1.56 (1.12 - 2.18)
Age at first cigarette[a]	
Early (<= 13 years)*	0.43 (0.25 - 0.73)
Late (>16 years)	0.76 (0.54 - 1.05)
Nicotine dependence risk group (based on paternal status)[b]	
Group 1: high G, high E*	1.66 (1.20 - 2.29)
Group 2: high G, low E	1.62 (1.00 - 2.61)
Group 3: moderate G, low E	1.36 (0.89 - 2.10)
Maternal nicotine dependence (Fagerstrom proxy)	1.05 (0.97 - 1.13)
Alcohol dependence risk group (based on paternal status)[b]	
Group 1: high G, high E	0.81 (0.61 - 1.07)
Group 2: high G, low E	0.96 (0.66 - 1.41)
Group 3: moderate G, low E	0.91 (0.62 - 1.35)
Early first cigarette X risk period up to 1 year after first cigarette[c*]	2.68 (1.40 - 5.13)
Early first cigarette X risk period 2-3 years after first cigarette[c*]	6.51 (3.17 - 13.32)

[a] Hazard ratios relative to median age at first cigarette (14-15 years)

[b] Hazard ratios relative to Group 4 (control)

[c] Interaction terms included in the model to adjust for violation of proportional hazard assumption for alcohol use and for early age at first cigarette.

* $p < .05$

Table 4

Cox proportional hazards model for transition time from regular smoking to onset of nicotine dependence(n = 332)

	Hazard Ratio (95% CI)
Panic disorder*	13.28 (4.12 - 42.75)
Social phobia*	4.78 (2.44 - 9.37)
Major depressive disorder*	4.31 (1.80 - 10.31)
Conduct disorder*	3.62 (2.11 - 6.23)
Oppositional defiant disorder*	2.32 (1.32 - 4.06)
Nicotine dependence risk group (based on paternal status)[a]	
Group 1: high G, high E	0.88 (0.47 - 1.64)
Group 2: high G, low E	0.36 (0.13 - 1.00)
Group 3: moderate G, low E	0.70 (0.23 - 2.16)
Maternal nicotine dependence (Fagerstrom proxy)	0.92 (0.77 - 1.10)
Alcohol dependence risk group (based on paternal status)[a]	
Group 1: high G, high E	0.81 (0.40 - 1.63)
Group 2: high G, low E	1.04 (0.42 - 2.57)
Group 3: moderate G, low E	1.42 (0.60 - 3.38)

[a] Hazard ratios relative to Group 4 (control)

* $p < .05$