Published in final edited form as:

Drug Alcohol Depend. 2011 November 1; 118(2-3): 444–451. doi:10.1016/j.drugalcdep.2011.05.002.

Strategies for characterizing complex phenotypes and environments: General and specific family environmental predictors of young adult tobacco dependence, alcohol use disorder, and co-occurring problems*

Jennifer A. Bailey^{**}, Karl G. Hill^{**}, Meredith C. Meacham^{**}, Susan E. Young^{***}, and J. David Hawkins

^{**}Social Development Research Group, University of Washington, Seattle; 9725 3rd Ave NE, Suite 401, Seattle, WA 98115, USA.

^{***}Institute for Behavioral Genetics, University of Colorado, Boulder; 447 UCB, Boulder, CO 80309, USA

Abstract

Background—Defining phenotypes in studies of tobacco and alcohol misuse is difficult because of the complexity of these behaviors and their strong association with each other and with other problem behaviors. The present paper suggests a strategy for addressing this issue by conceptualizing and partitioning variance in phenotypes into either *general* or *substance/behavior-specific*. The paper also applies the *general* or *substance/behavior-specific* conceptualization to environmental predictors of tobacco and alcohol misuse and other problem behaviors.

Methods—Data were drawn from the Seattle Social Development Project, a contemporary, ethnically diverse and gender balanced longitudinal panel including 808 participants. Latent variable modeling was used to partition variance in young adult (age 24) nicotine dependence, alcohol abuse and dependence, illicit drug abuse and dependence, involvement in crime, and engagement in HIV sexual risk behavior into general problem behavior and behavior-specific variance. Similarly, measures of general, drinking-specific, and smoking-specific adolescent family environment were constructed.

Results—Consistent with expectations, more positive general family environment during adolescence was associated with lower levels of shared variance in problem behaviors at age 24, but not with unique variance in tobacco or alcohol use disorder. Higher levels of family smoking and drinking environments during adolescence, however, were positively associated with unique variance in tobacco and alcohol use disorder, respectively, but did not predict shared variance in problem behaviors.

Conclusions—Results support the utility of the proposed approach. Ways in which this approach might contribute to future molecular genetic studies are discussed.

*Supplementary material for this article may be found by entering DOI...

© 2011 Elsevier Ireland Ltd. All rights reserved.

Corresponding Author: Jennifer A. Bailey, Social Development Research Group, University of Washington, Seattle, 9725 3rd Ave., NE, Suite 401, Seattle, WA 98115, jabailey@uw.edu, (phone) 1-206-616-9115, (fax) 1-206-543-4507.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

nicotine dependence; alcohol use disorder; phenotype definition; measuring environment for GxE research

1. Background

Adult tobacco and alcohol misuse are complex behaviors that are influenced by a combination of environmental and genetic factors (Kreek et al., 2005; Rutter et al., 2006), which also are complex. Researchers aiming to understand the etiology of adult tobacco and alcohol misuse are faced with the difficult task of measuring and defining these outcomes, or phenotypes, and of modeling a wide array of risk and protective factors from multiple domains. Further complicating research, tobacco and alcohol misuse are strongly correlated with each other and with a number of other problem behaviors. The present study builds on prior research focusing on the notion of general and specific variance in problem behaviors, as well as general and specific etiological factors. It aims to demonstrate how latent variable modeling can be used to partition variance in complex, multidimensional phenotypes and environment measures, and tests whether general family environment, family smoking environment, and family drinking environment in adolescence are differentially related to tobacco misuse, alcohol misuse, and general problem behavior at age 24.

1.1 Specification of complex tobacco and alcohol use phenotypes

The development of tobacco dependence and alcohol use disorders is intertwined (Hawkins et al., 2002; Hughes et al., 2000; Jackson et al., 2005). It has been well established that problem tobacco and alcohol use also share substantial variance with other forms of drug use (Bailey et al., 2006; Tsuang et al., 2001; Young et al., 2006; Kendler et al., 2003), crime, and HIV sexual risk behavior (Iacono et al., 1999; Young et al., 2000; Duncan et al., 1999; Bryan and Stallings, 2002). Sociological and criminological research has supported the notion of “general deviance,” and published findings in these fields suggest that up to 60% of variance in common problem behaviors may be shared (McGee and Newcomb, 1992; Newcomb and McGee, 1991; Osgood et al., 1988). Data from behavior genetic studies suggest that the shared variance among adolescent and young adult problem behaviors is highly heritable (Button et al., 2007; Hicks et al., 2004; McGue et al., 2006; Tsuang et al., 1998; Young et al., 2009). Molecular genetic studies have begun to identify specific genetic markers predictive of the problem use of multiple substances (Dick et al., 2010; Li et al., 2008; Philibert et al., 2009). Thus, findings from multiple fields of study all point to an overlap among substance use and other common problem behaviors in adolescence and young adulthood. Therefore, defining phenotypes that account for the co-occurrence of tobacco and alcohol misuse with other problem behaviors is both important and likely to prove fruitful.

Yet, prior research also suggests the presence of non negligible variance in problem tobacco and alcohol use and co-occurring behaviors that is unshared, or unique (Newcomb and McGee, 1991; Osgood et al., 1988). For example, Osgood and colleagues (1988) found that as much as 69% of variance in heavy alcohol use was not accounted for by general problem behavior. Hicks and colleagues (2004) found evidence for specific concordance in alcohol dependence and illicit drug dependence in addition to concordance in general externalizing behavior among adolescent twins. Kendler and colleagues (2003) found that substance-specific genetic liability accounted for 14% of the variance in alcohol dependence and 21% of the variance in other drug dependence among adult twins; evidence for a general genetic liability that contributed to multiple substance use and problem behaviors also emerged.

Therefore, phenotypes that consider unique or substance-specific variance in problem tobacco and alcohol use also are potentially useful.

In light of this, latent variable modeling, which can partition variance in substance use and related behaviors into general and substance-specific variance, may be particularly useful in defining phenotypes based on complex, multidimensional behaviors such as problem tobacco and alcohol use. Latent variable modeling has a long history in behavior genetic and addiction research, and has been used successfully in numerous studies to partition variance in problem behaviors. It allows the generation of complex phenotypes with many advantages, including greater specificity (e.g., isolating alcohol dependence risk that is independent of antisocial behavior or testing associations with shared variance, unique variance, or both simultaneously) and reliability (i.e., latent variables are free of measurement error that is inherent in observed variables). These features increase statistical power in a variety of circumstances, including in the presence of missing data (Medland and Neale, 2010).

1.2 Specification of the environment

Aspects of family, peer, school, neighborhood, and cultural environments all have been implicated in the development of problem substance use (Hawkins et al., 1992). Complex interactions among these environmental domains may be particularly important to consider (Bronfenbrenner, 1986; Catalano and Hawkins, 1996; Hawkins and Weis, 1985). Even within individual environmental domains such as the family, multiple etiological factors exist, making it difficult to include all relevant factors in statistical models. Here again, the use of latent variable modeling and the idea of general versus specific may be helpful. For example, some features of the family environment such as poor family management, low levels of bonding and involvement, and high levels of conflict (Hawkins et al., 1992; Skeer et al., 2009; Chung et al., 2002; Hill et al., 2010) have been linked with higher rates of substance use and other problem behaviors. Other types of familial factors such as parent and sibling drinking and parent attitudes favorable toward drinking may create an environment that encourages alcohol use specifically (Chassin et al., 1991; Kosterman et al., 2000). Similarly, parent and sibling smoking and other aspects of smoking-specific family environment may influence smoking (Andrews et al., 1997; Chassin et al., 2002; Foshee and Bauman, 1992; Hill et al., 2005), but not uniquely predict other problem behaviors. Latent variable modeling may be useful as a strategy for consolidating these measures of general and substance-specific environments, which often are highly intercorrelated (Hawkins et al., 1992). The present study describes an example of the use of latent variable modeling to create measures of complex phenotypes and environments that illustrates the utility of the general versus specific conceptualization. Two broad developmental periods are considered: outcomes in young adulthood (age 24) are linked to family general, smoking and drinking environments in adolescence (ages 10–18).

2. Methods

2.1 Participants and procedures

Participants were drawn from the Seattle Social Development Project (SSDP), a longitudinal study of the development of positive and antisocial behaviors. Sample members were recruited in the fall of 1985 from all fifth-grade students attending 18 Seattle elementary schools serving a mix of high- and lower crime neighborhoods ($N = 1053$). Of these students, 808 (77%) consented to take part in the study. The sample was gender balanced and ethnically diverse: 49% female; 47% white, 26% African American, 22% Asian American, 5% Native American. Because the number of Native American participants was

too small to permit reliable analyses, they were dropped, bringing the analysis sample size to 765.

Data used here were collected from students at ages 10–16, 18 and 24 years. Parents provided written consent and youth provided assent for data collected before age 18. After age 18, youth provided consent at each wave. Data collection procedures were approved by the University of Washington Institutional Review Board. About 95% (N = 752) of still living participants (n = 794) were retained at age 24, suggesting little risk for bias due to attrition.

2.2 Measures¹

2.2.1 General family environment—Indicators of general family environment included family management, family conflict, family positive involvement, and bonding to family members. Each construct was reported by youth, and measured yearly when youth were ages 10–18, except involvement, which was measured at ages 10–16; available measures were averaged across adolescence. For all general family environment scales, items were recoded as necessary so that higher scores indicated more of the construct (e.g., more bonding, more conflict).

2.2.2 Family drinking environment—Indicators of family drinking environment included parent and sibling drinking, parent drinking attitudes, and involvement of target youth in family member drinking (getting or opening a drink for a family member). Parents reported their own drinking, their partner's drinking, their attitudes toward drinking, and the involvement of the target child in family member drinking. Sibling drinking was reported by the target youth (scored as 1 *has drinking siblings* or 0 *no drinking siblings*). Respondents without siblings were scored as 0 because they had no drinking siblings. Measures of each construct were averaged across adolescence.

2.2.3 Family smoking environment—Family smoking environment measures included parent and sibling smoking, parent smoking attitudes, and involvement of youth in smoking (getting or lighting cigarettes for family members). One parent per family reported on their own smoking, their partner's smoking, their attitudes toward smoking, and the involvement of the target child in family member smoking. Similar to sibling drinking, sibling smoking was reported by target youth. Respondents without siblings were scored as 0 because they had no smoking siblings. Measures of each construct were averaged across adolescence.

2.2.4 Problem behaviors at age 24—Measured problem behaviors included tobacco dependence, alcohol abuse and dependence, illicit drug abuse and dependence, past year involvement in crime, and HIV sexual risk behavior. Tobacco, alcohol, and illicit drug use disorders were measured using the Diagnostic Interview Schedule (Robins et al., 1981). Count variables indexed the number of DSM-IV (American Psychiatric Association, 1994) criteria met for each disorder. High risk sexual behavior measures assessed multiple behaviors, including having multiple sex partners in the past year, using condoms inconsistently with one's last three partners, being involved in prostitution, and the frequency of engaging in sex after using alcohol or other drugs. Scores represented a count of the number of sex risk behaviors reported (possible range 0 – 4). Past year involvement in crime was measured by self-report. Participants responded to yes/no questions as to whether they had engaged in a series of minor delinquency, property crime, drug crime, and violent crime acts in the past year. The number of crimes reported was summed. As would be

¹Specific items used, response scales, exact ages of assessment, and reliabilities for general family environment, family drinking environment, and family smoking environment are available online as Supplementary Materials.

expected in a community sample, few respondents reported high numbers of drug abuse and dependence symptoms or criminal behaviors. Therefore, the drug abuse and dependence symptom counts and crime variety variables were truncated at 4 or more.

2.2.5 Control variables—Gender and ethnicity were self-reported. Childhood socioeconomic status was assessed by eligibility for the National School Lunch/School Breakfast program at any time in grades 5, 6, or 7, and was taken from school records.

2.3 Analysis

Correlation coefficients and structural equation models were estimated using Mplus version 5.2 (Schafer and Graham, 2002; Muthén and Muthén, 1998–2007). Categorical variables, including the measures of problem behaviors at age 24, were specified as such for both types of analysis, and the WLSMV estimator was used (Muthén and Muthén, 1998–2007). Full Information Maximum Likelihood estimation was used to minimize bias due to missing data; 949 (6%) of 16,065 data points (765 respondents $\times$ 21 variables) were missing. First, a confirmatory factor analysis including the family general, smoking, and drinking environments and shared variance in problem behaviors latent factors was estimated in order to determine the zero order associations among latent variables. Second, a model testing hypothesized structural paths was estimated. A third model included control variables (gender, childhood poverty, ethnicity) to determine whether significant associations observed in Model 2 remained significant.

Study hypotheses rely on separating variance in nicotine and alcohol criteria into that associated with other problem behaviors and that which is independent of other problem behaviors, or the residual variance. These variables were ordered-categorical (0 to 4+ behaviors/symptoms), however, and residual variances are not estimated for categorical variables in Mplus (Muthén and Muthén, 1998–2007). In order to predict residual variances for the categorical problem behaviors indicators, Mplus required the creation of phantom latent variables for each of the categorical problem behavior indicators. These were created following procedures recommended by Muthén (Muthén, 2006; see also Bentler and Raykov, 2000), and Theta parameterization was specified. The variance of these phantom latent variables was then partitioned into shared variance among problem behaviors and unique, residual variance. For ease of interpretation, Figures are presented without the phantom variables; the syntax used to specify the final model is available in the online Supplementary Materials².

3. Results

3.1 Descriptive findings

Table 1 shows descriptive information about problem behaviors in the sample. Symptoms of alcohol use disorder or nicotine dependence and engagement in 1 or more HIV sexual risk behaviors were common. Results of correlation analysis including the family environment and young adult problem behavior indicator variables are presented in Table 2. Patterns of association were consistent with hypothesized latent constructs: the general family environment indicators (family management, conflict, positive involvement, bonding) were significantly and moderately associated with one another (range of absolute value of $r = .45$ to $.65$), as were the young adult problem behaviors indicators (HIV sex risk behavior, crime, AUD criteria, ND criteria, IDUD criteria; range of absolute value of $r = .20$ to $.62$). Associations among family smoking environment indicators (parent smoking, sibling

²Specific items used, response scales, exact ages of assessment, and reliabilities for general family environment, family drinking environment, and family smoking environment are available online as Supplementary Materials

smoking, parental attitudes toward adolescent smoking, involvement in parent smoking) and family drinking environment indicators (parent drinking, sibling drinking, parental attitudes toward adolescent drinking, involvement in parent drinking) were small to moderate (range of absolute value of $r = .01$ to $.50$). Sibling drinking and sibling smoking ($r = .63$) and parental attitudes permissive of adolescent smoking and drinking ($r = .61$) were moderately associated. General family environment measures were associated with indicators of young adult problem behaviors. Small but significant associations between family smoking environment variables and nicotine dependence criteria and between family drinking environment and alcohol use disorder criteria also were observed.

3.2 Structural equation models

A confirmatory factor analysis testing the hypothesized family smoking environment, family drinking environment, general family environment, and comorbid outcomes latent factors was estimated (see Table 3). Associations between the residual variances of sibling smoking and sibling drinking and between the residual variances of parental attitudes permissive of adolescent smoking and drinking were included based on modification indices. Model fit following these two adjustments was acceptable [$\chi^2(50) = 132.82, p < .05, CFI = .93, TLI = .93, RMSEA = .05, WRMR = 1.10$]. All indicators loaded significantly on their respective factor (Table 3). The shared variance in problem behaviors factor accounted for between 36% and 87% of the variance in the individual problem behaviors. Associations among latent factors also are presented in Table 3. General family environment was not significantly related to either family smoking or family drinking environment. All three family environment latent factors were significantly associated with the shared variance in problem behaviors latent factor.

Figure 1 depicts a model testing hypothesized structural relationships among latent variables. Consistent with study hypotheses, results showed that adolescent general family environment predicted comorbid outcomes, but was not significantly associated with residual variance in alcohol criteria, nicotine criteria, illicit drug criteria, crime, or sexual risk behavior. Adolescent family smoking environment predicted residual variance in age 24 nicotine dependence, and adolescent family drinking environment predicted residual variance in alcohol criteria at age 24. Associations between family smoking environment and family drinking environment and residual variance in other indicators of problem behaviors were tested and were not significant. The final model included only significant paths. Model fit was acceptable [$\chi^2(48) = 116.25, p < .05, CFI = .94, TLI = .94, RMSEA = .04, WRMR = 1.07$].

Figure 2 shows results of the estimation of a model including controls. Results show that the inclusion of controls did not reduce any previously significant structural paths to nonsignificance. Male gender was associated with higher levels of shared variance in problem behaviors and poorer general family environment. Receipt of free or reduced-price lunch in childhood was associated with higher levels of shared variance in problem behaviors, poorer general family environment, lower family drinking environment, and higher family smoking environment. Asian Americans reported lower levels of shared variance in problem behaviors and lower family smoking environment compared to Caucasians (reference group). Both African Americans and Asian Americans reported lower family drinking environments compared to Caucasians. Significant associations among control variables (African American with poverty $r = .29$, Asian American with poverty $r = .18$, Asian American with African American $r = -.34$) are not shown in the figure to improve readability. Model fit was acceptable [$\chi^2(73) = 208.72, p < .05, CFI = .91, TLI = .91, RMSEA = .05, WRMR = 1.12$].

4. Discussion

This study sought to use latent variable modeling to test the utility of conceptualizing both predictors and outcomes in terms of general and behavior-specific variance to examine the contribution of family environmental factors to tobacco misuse, alcohol misuse, and other problem behaviors. We sought to partition the variance in common young adult problem behaviors into that which is shared and that which is unique to each behavior and to determine the degree to which adolescent general family environment, family smoking environment, and family drinking environment predict the common and specific variance in young adult problem behaviors. Consistent with expectations, more positive general family environment during adolescence was associated with lower levels of shared variance in problem behaviors at age 24, but not with unique variance in tobacco or alcohol use disorder. Higher levels of family smoking and drinking environments during adolescence were positively associated with unique variance in tobacco and alcohol use disorders, respectively, but did not predict shared variance in problem behaviors.

As expected, nicotine dependence symptomatology, alcohol and illicit drug abuse and dependence symptomatology, involvement in crime, and HIV sexual risk behavior at age 24 loaded strongly and significantly on a single latent problem behavior factor. Together with previous findings suggesting both common and specific variance among problem behaviors (Costello, 2007; Iacono et al., 1999; Young et al., 2000; Duncan et al., 1999; Bryan and Stallings, 2002; Kendler et al., 2003) and common and specific genetic contributions to these behaviors (Button et al., 2007; Dick et al., 2010; Hicks et al., 2004; Li et al., 2008; McGue et al., 2006; Philibert et al., 2009; Young et al., 2009), the present results support the utility of considering multiple problem behaviors when constructing phenotype measures. Such models reflect the co-occurrence among problem behaviors, while allowing researchers to model unique variance in a particular behavior. Measuring multiple problem behaviors and partitioning their variance into general and specific for etiological analyses affords several advantages. First, partitioning variance in this way may lead to greater consistency in etiological studies. For example, studies aiming to identify risk and protective factors specific to problem nicotine use may benefit from partitioning out variance in nicotine use disorder that is associated with problem behavior. Alternatively, identifying risk and protective factors that contribute to a range of problem behaviors may provide cost-effective prevention and intervention targets. Finally, using latent variable modeling to isolate the variance specific to a behavior or drug of interest may reduce the need to recruit samples free of comorbidity, making sample selection easier.

Findings also supported the utility of dividing adolescent family environments into general environment, smoking-specific environment, and drinking-specific environment. The present results are consistent with prior work suggesting that both general and substance-specific aspects of the family environment are related to later problem substance use (Chassin et al., 1998; Hill et al., 2005; Peterson et al., 1994). Organizing measures of the family environment into general and substance-specific revealed that general problem behavior was best explained by general family environment, whereas unique variance in young adult tobacco and alcohol use disorders was best predicted by tobacco and alcohol specific family environmental factors, respectively, including family member use and parental attitudes toward adolescent tobacco or alcohol use. We were able to combine multiple, repeated measures of each aspect of the family environment, demonstrating the utility of the method for creating simplified environment measures that still were longitudinal and multidimensional. The latent variable method employed here also allowed for modeling of associations among environment measures and control variables.

4.1 Future directions: Integrating genetic markers

The SSDP study has collected and is currently genotyping participant DNA. Although genetic data were not yet available to inform this study, the models used here reflect our thinking about phenotype and environment measures that may be useful in molecular genetic studies of gene-environment interaction. Latent variable modeling and the notion of general versus specific influences and outcomes address two potential roadblocks to studying the interplay of genes and environment in research on problem substance use identified at meetings on gene-environment interaction research sponsored by National Institute on Alcohol Abuse and Alcoholism (NIAAA; cf. Gunzerath and Goldman, 2003) and the National Institute on Drug Abuse (NIDA; cf. Conway et al., 2006): the specification of appropriate models of substance use phenotypes, and the specification of models of the environment suitable for the study of gene-environment interplay. In studies aiming to identify genetic markers unique to problem nicotine use, latent variable approaches could be used to partition out variance in nicotine use disorder that is associated with problem behavior, possibly resulting in greater consistency across studies. Using latent variable modeling to consolidate multidimensional measures of the environment could allow the inclusion of complex environmental measures in gene-environment interaction analyses without grossly exacerbating multiple testing issues.

Figure 3 depicts a hypothetical model suitable for including a small number of genetic markers or genetic risk scores summarizing multiple relevant polymorphisms associated with nicotine metabolism and dopamine dysregulation. As shown in the model, direct effects of genetic markers on both shared variance in problem behaviors and unique variance in nicotine dependence could be tested. Gene-environment correlation could be modeled by adding causal paths from genetic markers to environmental variables. Finally, gene-environment interactions could be tested using multiplicative interaction terms or multiple group modeling.

In spite of the existence of models for conducting research on gene-environment interaction presented here and elsewhere (Brody et al., 2009; Moffitt et al., 2005; van der Zwaluw et al., 2010), the challenges to be overcome are substantial. Such research requires interdisciplinary teams that include genetic and statistical expertise. Ethnic diversity among sample members raises the possibility of spurious findings due to differential allele frequency. The effects of any specific polymorphism on complex behaviors such as tobacco and alcohol misuse are likely to be quite small, given the many causal links in the chain from DNA to behavior. Strategies still need to be developed that summarize genetic influence in a similarly parsimonious yet powerful manner, for example by employing gene-set (Liu et al., 2010; Peng et al., 2010) or pathway-based approaches (De la Cruz et al., 2010; Wang et al., 2007), as opposed to focusing on the effects of single polymorphisms.

4.2 Limitations

Some limitations should be kept in mind when interpreting the present results. First, measures of adolescent family environment were averaged across late childhood and adolescence. This study does not, therefore, provide information on the influence of family environmental characteristics during more circumscribed developmental periods (e.g., middle school versus high school). Second, this study relied on self-reports of substance use disorders, crime, and HIV sexual risk behavior that may be susceptible to social desirability bias. Substance use disorders were assessed with a widely-used, standardized questionnaire, however, and prior research supports the validity of self reports of risk behaviors (Patrick et al., 1994), especially in the context of longitudinal studies where participants have established rapport and trust with investigators. Further, questions about sexual behavior were self-administered, reducing pressure for socially desirable responding.

4.3 Prevention implications and conclusions

Results suggest that prevention programs addressing general family functioning can have beneficial effects on a number of young adult problem behaviors, including tobacco and alcohol use disorders. A growing number of drug prevention and positive youth development programs have found beneficial effects on other problem behaviors, including risky sexual behavior, STI acquisition, teen pregnancy, drug and alcohol use, violent delinquency, and school misbehavior (Ellickson et al., 2009; Gavin et al., 2010; Hawkins et al., 1999). Knowledge about environmental influences that affect multiple problem behaviors, such as general adolescent family environment, aids in the targeting of preventive and treatment interventions. Further, addressing common causes for multiple problem behaviors may improve the efficiency and cost-effectiveness of prevention and treatment programs (Bailey, 2009).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

- American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th Ed.. Washington, DC: American Psychiatric Association; 1994.
- Andrews JA, Hops H, Duncan SC. Adolescent modeling of parent substance use: the moderating effect of the relationship with the parent. *J. Fam. Psychol.* 1997; 11:259–270.
- Bailey JA. Addressing common risk and protective factors can prevent a wide range of adolescent risk behaviors. *J. Adolesc. Health.* 2009; 45:107–108. [PubMed: 19628134]
- Bailey JA, Hill KG, Oesterle S, Hawkins JD. Linking substance use and problem behavior across three generations. *J. Abnorm. Child Psychol.* 2006; 34:273–292.
- Bentler PM, Raykov T. On measures of explained variance in nonrecursive structural equation models. *J. Applied Psychol.* 2000; 85:125–131. [PubMed: 10740963]
- Brody GH, Chen Y, Beach SRH, Philibert RA, Kogan SM. Participation in a family-centered prevention program decreases genetic risk for adolescents' risky behaviors. *Pediatrics.* 2009; 124:911–917. [PubMed: 19706565]
- Bronfenbrenner U. Ecology of the family as a context for human development: research perspectives. *Dev. Psychol.* 1986; 22:723–742.
- Bryan A, Stallings MC. A case control study of adolescent risky sexual behavior and its relationship to personality dimensions, conduct disorder, and substance use. *J. Youth Adolesc.* 2002; 31:387–396.
- Button TMM, Rhee SH, Hewitt JK, Young SE, Corley RP, Stallings MC. The role of conduct disorder in explaining the comorbidity between alcohol and illicit drug dependence in adolescence. *Drug Alcohol Depend.* 2007; 87:46–53. [PubMed: 16956733]
- Catalano, RF.; Hawkins, JD. The social development model: a theory of antisocial behavior. In: Hawkins, JD., editor. *Delinquency and Crime: Current Theories*. New York: Cambridge University Press; 1996. p. 149-197.
- Chassin L, Presson CC, Rose JS, Sherman SJ, Prost J. Parental smoking cessation and adolescent smoking. *J. Pediatr. Psychol.* 2002; 27:485–496. [PubMed: 12177249]
- Chassin L, Presson CC, Todd M, Rose JS, Sherman SJ. Maternal socialization of adolescent smoking: the intergenerational transmission of parenting and smoking. *Dev. Psychol.* 1998; 34:1189–1201. [PubMed: 9823504]
- Chassin L, Rogosch F, Barrera M. Substance use and symptomatology among adolescent children of alcoholics. *J. Abnorm. Psychol.* 1991; 100:449–463. [PubMed: 1757658]
- Chung JJ, Hawkins JD, Gilchrist LD, Hill KG, Nagin DS. Identifying and predicting offending trajectories among poor children. *Soc. Serv. Rev.* 2002; 76:663–685. [PubMed: 17848977]
- Conway KP, Compton WM, Miller PM. Novel approaches to phenotyping drug abuse. *Addict. Behav.* 2006; 31:923–928.

- Costello E. Psychiatric predictors of adolescent and young adult drug use and abuse: what have we learned? *Drug Alcohol Depend.* 2007; 88S:S97–S99. [PubMed: 17276625]
- De la Cruz O, Wen X, Ke B, Song M, Nicolae D. Gene, region and pathway level analyses in whole-genome studies. *Genet. Epidemiol.* 2010; 34:222–231. [PubMed: 20013942]
- Dick DM, Meyers J, Aliev F, Nurnberger J Jr, Kramer J, Kuperman S, Porjesz B, Tischfield J, Edenberg HJ, Foroud T, Schuckit M, Goate A, Hesselbrock V, Bierut LJ. Evidence for genes on chromosome 2 contributing to alcohol dependence with conduct disorder and suicide attempts. *Am. J. Med. Genet.* 2010;1179–1188. Part B 153B. [PubMed: 20468071]
- Duncan SC, Strycker LA, Duncan TE. Exploring associations in developmental trends of adolescent substance use and risky sexual behavior in a high-risk population. *J. Behav. Med.* 1999; 22:21–34. [PubMed: 10196727]
- Ellickson PL, McCaffrey DF, Klein DJ. Long-term effects of drug prevention on risky sexual behavior among young adults. *J. Adolesc. Health.* 2009; 45:111–117. [PubMed: 19628136]
- Foshee V, Bauman KE. Parental and peer characteristics as modifiers of the bond-behavior relationship: an elaboration of control theory. *J. Health Soc. Behav.* 1992; 33:66–76. [PubMed: 1619259]
- Gavin LE, Catalano RF, David-Ferdon C, Gloppen KM, Markham CM. A review of positive youth development programs that promote adolescent sexual and reproductive health. *J. Adolesc. Health.* 2010; 46:S75–S91. [PubMed: 20172462]
- Gunzerath L, Goldman D. G x E: A NIAAA workshop on gene-environment interactions. *Alcohol. Clin. Exp. Res.* 2003; 27:540–562. [PubMed: 12658122]
- Hawkins JD, Catalano RF, Kosterman R, Abbott R, Hill KG. Preventing adolescent health-risk behaviors by strengthening protection during childhood. *Arch. Pediatr. Adolesc. Med.* 1999; 153:226–234. [PubMed: 10086398]
- Hawkins JD, Catalano RF, Miller JY. Risk and protective factors for alcohol and other drug problems in adolescence and early adulthood: implications for substance-abuse prevention. *Psychol. Bull.* 1992; 112:64–105. [PubMed: 1529040]
- Hawkins, JD.; Hill, KG.; Guo, J.; Battin-Pearson, SR. Substance use norms and transitions in substance use: implications for the gateway hypothesis. In: Kandel, DB., editor. *Stages and Pathways of Drug Involvement. Examining the Gateway Hypothesis.* New York: Cambridge University Press; 2002. p. 42-64.
- Hawkins JD, Weis JG. The social development model: an integrated approach to delinquency prevention. *J. Primary Prev.* 1985; 6:73–97.
- Hicks BM, Krueger RF, Iacono WG, McGue M, Patrick CJ. Family transmission and heritability of externalizing disorders. *Arch. Gen. Psychiatry.* 2004; 61:922–928. [PubMed: 15351771]
- Hill KG, Hawkins JD, Bailey JA, Catalano RF, Abbott RD, Shapiro V. Person-environment interaction in the prediction of alcohol abuse and alcohol dependence in adulthood. *Drug Alcohol Depend.* 2010; 110:62–69. [PubMed: 20299164]
- Hill KG, Hawkins JD, Catalano RF, Abbott R, Guo J. Family influences on the risk of daily smoking initiation. *J. Adolesc. Health.* 2005; 37:202–210. [PubMed: 16109339]
- Hughes JR, Oliveto AH, MacLaughlin M. Is dependence on one drug associated with dependence on other drugs? The cases of alcohol, caffeine and nicotine. *Am. J. Addict.* 2000; 9:196–201. [PubMed: 11000915]
- Iacono WG, Carlson SR, Taylor J, Elkins IJ, McGue M. Behavioral disinhibition and the development of substance-use disorders: findings from the Minnesota Twin Family Study. *Dev. Psychopathol.* 1999; 11:869–900. [PubMed: 10624730]
- Jackson KM, Sher KJ, Schulenberg JE. Conjoint developmental trajectories of young adult alcohol and tobacco use. *J. Abnorm. Psychol.* 2005; 114:612–626. [PubMed: 16351384]
- 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.* 2003; 60:929–937. [PubMed: 12963675]
- Kosterman R, Hawkins JD, Guo J, Catalano RF, Abbott R. The dynamics of alcohol and marijuana initiation: patterns and predictors of first use in adolescence. *Am. J. Public Health.* 2000; 90:360–366. [PubMed: 10705852]

- Kreek MJ, Nielsen DA, Butelman ER, La Forge KS. Genetic influences on impulsivity, risk taking, stress responsivity and vulnerability to drug abuse and addiction. *Nature Neurosci.* 2005; 8:1450–1457. [PubMed: 16251987]
- Li CY, Mao X, Wei L. Genes and (common) pathways underlying drug addiction. *PLoS Computat. Biol.* 2008; 4:e2.
- Liu J, McRae A, Nyholt D, Medland S, Wray N, Brown K, Hayward N, Montgomery G, Visscher P, Martin N, Macgregor S. AMFS Investigators. A versatile gene-based test for genome-wide association studies. *Am. J. Human Genet.* 2010; 13:179–193.
- McGee L, Newcomb MD. General deviance syndrome: expanded hierarchical evaluations at four ages from early adolescence to adulthood. *J. Consult. Clin. Psychol.* 1992; 60:766–776. [PubMed: 1401392]
- McGue M, Iacono WG, Krueger RF. The association of early adolescent problem behavior and adult psychopathology: a multivariate behavioral genetic perspective. *Behav. Genet.* 2006; 36:591–602. [PubMed: 16557361]
- Medland SE, Neale MC. An integrated phenomic approach to multivariate allelic association. *Eur. J. Human. Genet.* 2010; 18:233–239. [PubMed: 19707246]
- Moffitt TE, Caspi A, Rutter M. Strategy for investigating interactions between measured genes and measured environments. *Arch. Gen. Psychiatry.* 2005; 62:473–481. [PubMed: 15867100]
- Muthén BO. Reply to P. Sturgis on the Mplus Discussion Board. 2006
- Muthén, LK.; Muthén, BO. *Mplus user's guide*. Los Angeles: Muthén and Muthén; 1998–2007.
- Newcomb MD, McGee L. Influence of sensation seeking on general deviance and specific problem behaviors from adolescence to young adulthood. *J. Pers. Soc. Psychol.* 1991; 61:614–628. [PubMed: 1960653]
- Osgood DW, Johnston LD, O'Malley PM, Bachman JG. The generality of deviance in late adolescence and early adulthood. *Am. Sociol. Rev.* 1988; 53:81–93.
- Patrick DL, Cheadle A, Thompson DC, Diehr P, Koepsell T, Kinne S. The validity of self-reported smoking: a review and meta-analysis. *Am. J. Public Health.* 1994; 84:1086–1093. [PubMed: 8017530]
- Peng G, Luo L, Siu H, Zhu Y, Hu P, Hong S, Zhao J, Zhou X, Reveille J, Jin L, Amos C, Xiong M. Gene and pathway-based second-wave analysis of genome-wide association studies. *Eur. J. Human Genet.* 2010; 18:111–117. [PubMed: 19584899]
- Peterson PL, Hawkins JD, Abbott R, Catalano RF. Disentangling the effects of parental drinking, family management, and parental alcohol norms on current drinking by Black and White adolescents. *J. Res. Adolesc.* 1994; 4:203–227.
- Philibert RA, Gunter TD, Beach SRH, Brody GH, Nollenbeck N, Andersen A, Adams W. Role of GABRA2 on risk for alcohol, nicotine, and cannabis dependence in the Iowa Adoption Studies. *Psychiatr. Genet.* 2009; 19:91–98. [PubMed: 19672139]
- Robins, LN.; Helzer, JE.; Croughan, J.; Williams, JBW.; Spitzer, RL. *NIMH Diagnostic Interview Schedule: Version III* (May 1981). Rockville, MD: National Institute of Mental Health; 1981.
- Rutter M, Moffitt TE, Caspi A. Gene-environment interplay and psychopathology: multiple varieties but real effects. *J. Child Psychol. Psychiatry.* 2006; 47:226–261. [PubMed: 16492258]
- Schafer JL, Graham JW. Missing data: Our view of the state of the art. *Psychol Methods.* 2002; 7:147–177. [PubMed: 12090408]
- Skær M, McCormick MC, Normand SLT, Buka SL, Gilman SE. A prospective study of familial conflict, psychological stress, and the development of substance use disorders in adolescence. *Drug Alcohol Depend.* 2009; 104:65–72. [PubMed: 19446409]
- Tsuang MT, Bar JL, Harley RM, Lyons MJ. The Harvard Twin Study of Substance Abuse: what we have learned. *Harvard Rev. Psychiatry.* 2001; 9:267–279.
- Tsuang MT, Lyons MJ, Meyer JM, Doyle T, Eisen SA, Goldberg J, True W, Lin N, Toomey R, Eaves L. Co-occurrence of abuse of different drugs in men: the role of drug-specific and shared vulnerabilities. *Arch. Gen. Psychiatry.* 1998; 55:967–972. [PubMed: 9819064]
- van der Zwaluw CS, Engels RCME, Vermulst AA, Franke B, Buitelaar JK, Verkes RJ, Scholte RHJ. Interaction between dopamine D2 receptor genotype and parental rule-setting in adolescent

alcohol use: evidence for a gene-parenting interaction. *Mol. Psychiatry*. 2010; 15:727–735. [PubMed: 19238152]

Wang K, Li M, Bucan M. Pathway-based approaches for analysis of genomewide association studies. *Am. J. Human Genet*. 2007; 81:1278–1283. [PubMed: 17966091]

Young SE, Friedman NP, Miyake A, Willcutt EG, Corley RP, Haberstick BC, Hewitt JK. Behavioral disinhibition: liability for externalizing spectrum disorders and its genetic and environmental relation to response inhibition across adolescence. *J. Abnorm. Psychol*. 2009; 118:117–130. [PubMed: 19222319]

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

Young SE, Stallings MC, Corley RP, Krauter KS, Hewitt JK. Genetic and environmental influences on behavioral disinhibition. *Am. J. Med. Genet*. 2000; 96:684–695. [PubMed: 11054778]

Figure 1.

Model showing structural associations among latent constructs without control variables. All structural paths estimated in the final model are shown in the figure. Omitted paths were not significant in preliminary models and were dropped.

Figure 2. Model showing structural associations among latent constructs with control variables. All structural paths estimated in the final model are shown in the figure; correlation coefficients among control variables are presented in the text. Omitted paths were not significant in preliminary models and were dropped.

Figure 3. Hypothetical model including genetic markers. NOTE: rGE = gene-environment correlation, GxE = gene-environment interaction. Boxes indicate measured variables and circles indicate latent (unmeasured) variables. Single-headed arrows indicate direct effects or causal associations (e.g., A). Single-headed arrows pointing to lines represent interactions (e.g., B). Small circles with single-headed arrows pointing to measured variables indicate residual variances (e.g., C).

Table 1

Descriptive information on age 24 problem behaviors.

Behavior	Mean (<i>SD</i>)	1+ symptoms/ behaviors (%)	4+ symptoms/ behaviors (%)
AUD criteria	.92 (1.31)	42%	8%
ND criteria	.60 (.98)	44%	2%
IDUD criteria	.38 (1.01)	16%	5%
Crime	.40 (.91)	22%	3%
HIV sex risk behavior	.63 (.79)	47%	< 1%

NOTE: AUD = alcohol use disorder, ND = nicotine dependence, IDUD = illicit drug use disorder, HIV = human immunodeficiency virus.

Table 2

Correlations among study variables.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. Family management	-															
2. Family conflict	-.65*	-														
3. Positive Involvement	.58*	-.45*	-													
4. Bonding	.63*	-.55*	.58*	-												
5. Sibling Smoking	-.10*	.14*	-.06	-.08*	-											
6. Parent Smoking	.05	.05	.06	.02	.18*	-										
7. Pro smoking attitudes	.07	-.02	.03	.06	.12*	.34*	-									
8. Involvement in parent smoking	<.01	.04	<.01	-.03	.13*	.42*	.22*	-								
9. Parent drinking	.02	.04	.06	-.04	.09*	.25*	.23*	.15*	-							
10. Sibling drinking	-.13*	.20*	-.04	-.08	.63*	.06	.03	.06	.11*	-						
11. Pro drinking attitudes	.05	-.02	.06	.01	-.01	.07	.61*	.09*	.38*	.01	-					
12. Involvement in parent drinking	.01	.11*	.06	-.05	.05	.13*	.16*	.13*	.50*	.10*	.33*	-				
13. HIV sex risk behavior	-.15*	.13*	-.08	-.10*	-.01	.03	.10*	-.02	.05	-.01	.08	.04	-			
14. Crime	-.24*	.22*	-.10*	-.16*	<.01	.05	.03	-.03	.03	.07	<.01	.05	.50*	-		
15. AUD criteria	-.16*	.15*	-.04	-.12*	.03	.08	.07	.01	.11*	.05	.10*	.08	.45*	.39*	-	
16. ND criteria	-.16*	.18*	-.05	-.13*	.13*	.17*	.07	.15*	.02	.08	-.04	.09	.21*	.20*	.38*	-
17. IDUD criteria	-.19*	.23*	-.08	-.16*	.07	.06	<.01	-.04	.02	.13*	-.01	.10	.62*	.61*	.55*	.43*

*
 $p < .05$

NOTE: HIV = human immunodeficiency virus, AUD = alcohol use disorder, ND = nicotine dependence, IDUD = illicit drug use disorder.

Table 3

Factor loadings and correlations among latent factors from CFA.

	Standardized Estimate (SE)	Unstandardized Estimate (SE)
<i>Factor loadings</i>		
Family general environment		
Family management	.87 (.02) *	.29 (.01)
Conflict	-.74 (.02) *	-.39 (.02)
Positive involvement	.65 (.03) *	.23 (.01)
Bonding	.77 (.02) *	.36 (.02)
Family drinking environment		
Pro drinking attitudes	.43 (.04) *	.20 (.02)
Parent drinking	.85 (.05) *	.57 (.04)
Sibling drinking	.15 (.04) *	.05 (.02)
Involvement in parent drinking	.62 (.05) *	.24 (.03)
Family smoking environment		
Pro smoking attitudes	.50 (.04) *	.24 (.02)
Parent smoking	.74 (.05) *	.92 (.08)
Sibling smoking	.24 (.04) *	.07 (.01)
Involvement in parent smoking	.51 (.04) *	.25 (.02)
Shared variance in problem behaviors		
Alcohol use disorder criteria	.77 (.03) *	1.22 (.13)
Nicotine dependence criteria	.60 (.05) *	.76 (.10)
Illicit drug use disorder criteria	.93 (.02) *	2.62 (.52)
Crime	.79 (.03) *	1.30 (.15)
Sex risk behavior	.78 (.03) *	1.25 (.13)
<i>Factor correlations</i>		
Family general environment w/ Family drinking environment	-.01 (.05)	-.01 (.05)
Family smoking environment	.01 (.05)	.01 (.05)
Family drinking environment w/ Family smoking environment	.39 (.05) *	.39 (.05)
Shared variance in problem behaviors w/ Family general environment	-.28 (.05) *	-.28 (.05)
Family drinking environment	.15 (.06) *	.15 (.06)
Family smoking environment	.13 (.06) *	.13 (.06)
<i>Indicator correlations</i>		
Sibling smoking w/ Sibling drinking	.64 (.03) *	.07 (.01)
Pro smoking attitudes w/ Pro drinking attitudes	.67 (.03) *	.12 (.01)

*
 $p < .05$

NOTE: The shared variance in problem behaviors factor is a second-order factor. Its indicators are the phantom latent variables representing the categorical problem behaviors measures. Regressions of the categorical problem behaviors measures on their respective phantom variables are fixed at 1.