

Searching for Interactive Effects in the Etiology of Early-Onset Substance Use

Lisa N. Legrand;^{1,2} Matt McGue,¹ and William G. Iacono¹

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This study sought to expand the modest literature investigating gene x environment interactions in the prediction of substance use. Our sample consisted of 591 male twins from the Minnesota Twin Family Study. Their relative genetic risk was estimated from their parents' substance-related diagnoses and their environmental risk from their affiliations at age 11 with social groups likely to either encourage or discourage substance use. At age 14, the boys' own substance use was assessed. We hypothesized both main effects and an interaction between our genetic- and environmental-risk variables in the prediction of substance use by this young age. We further theorized that the boys' inherited risk might take the form of temperament, specifically externalizing tendencies. Using regression analyses and biometrical modeling, we corroborated earlier research by finding evidence for a significant interactive effect in the etiology of substance use. Our results suggest that low levels of environmental risk may buffer against the potentially unfavorable effects of high familial risk; however, when environmental risk is high, the degree of familial risk is consequential. We were not able to support our second hypothesis; rather, temperament predicted substance use only through shared environmental factors.

KEY WORDS: Early-onset substance use; etiology; male twins; Minnesota Twin Family Study; prediction; temperament gene x environment interactions; genetic risk.

INTRODUCTION

Social scientists have long disputed which parental influences are of paramount importance in determining offspring characteristics: those passed on biologically or those transmitted through the family environment. Summarily termed the "nature versus nurture" debate, this spirited controversy historically has found researchers resolutely aligned with one side or the other. While allegiances may have shifted somewhat by topic and by time, it is only recently that a true rapprochement has begun to evolve between the two sides. A newer phrase, "nature via nurture" (Bouchard *et al.*, 1990, p. 228), aptly captures the increasing realization that for most human behaviors and characteristics, genetic and environmental influences are more complementary than competitive.

Perhaps psychopathology develops when inherited vulnerabilities combine additively with environmental risks to push an individual over a putative disease threshold. Alternatively, perhaps genetic factors modify an organism's responsiveness to its environment. If the latter occurs, genetically increased sensitivities or immunities to pathogenic aspects of the environment will give rise to gene x environment interactions.

The possibility of such interactions between genetic and environmental risks is especially intriguing to behavioral geneticists, for it could help explain a curious but consistent finding. Contrary to intuition, the environments shared by siblings seem to be largely without etiological significance for most individual differences in personality, cognition, and even psychopathology (Plomin and Daniels, 1987). This initially quite surprising finding may be interpreted as implying that social units such as the family have little to no effect on psychological functioning. On the

¹ Department of Psychology, University of Minnesota, 75 East River Road, Minneapolis, Minnesota 55455.

² To whom correspondence should be addressed. e-mail: llegendr@tfs.psych.umn.edu.

other hand, if gene x environment interactions are at work, this finding may simply mean that familial influences are rarely uniform across members (Kendler, 1995). This would be the case if responses to apparently similar environmental pressures were differentially influenced by personal genotypes.

Evidence for gene x environment interactions in the genesis of common psychological difficulties such as alcoholism (Cloninger et al., 1981; Cutrona et al., 1994) and conduct disorder (Cadoret et al., 1983, 1995) exists in cross-fostering studies. It appears that the coupling of a genetic diathesis with a high-risk environment leads to greater pathology than would be expected from either factor alone or both in additive combination. Unfortunately, the quantity of research on interactions remains limited, and thus our knowledge is only tentative regarding how inherited predispositions may interact with environmental risks to create psychological disorders.

This study seeks to expand the scope of existing literature by investigating possible interactions that may underlie the etiology of early-onset substance use. Using the youngest male cohort of the Minnesota Twin Family Study (MTFS), both genetic and environmental risk were estimated. Then, 3 years later, when the boys were 14, their substance use was assessed. It was anticipated that both the genetic-risk variable and the environmental-risk variable would independently predict early-onset use and that their interaction would be associated with an especially high risk for substance use.

Early-onset use is a variable of particular interest because it is a consistent, strong predictor of substance-related problems (Grant and Dawson, 1997; Hawkins et al., 1992). Most notably, substance use prior to age 15 is linked to an increased susceptibility for later abuse. Early use also forecasts more consistent use and the use of a broader array of substances (Kandel, 1982). Because of this established relationship, early use identifies those young adolescents who are at greatest risk for developing substance-related difficulties by adulthood.

There are some obvious limitations to our approach. Within our sample, genetic risk is only inferred from parental diagnoses. Furthermore, because we are using nonadoptive families, there is no clean separation between genetic and environmental influences. Most of the boys in our sample are being raised by both biological parents and thus their genetic risk may be confounded with environmental risks. Throughout much of this paper we refer to our genetic risk vari-

able as "familial risk" to acknowledge this concern. There are also genetic influences upon our environmental-risk measures, given that they involve some choices of affiliation and attachment. Notwithstanding these caveats, positive results *will be consistent with* the existence of a gene x environment interaction in the development of early-onset substance use.

We additionally investigated whether the genetic- or familial-risk variable might be replaced by a more proximal measure of risk: the boys' temperaments. We theorized that perhaps what are being transmitted from parent to child are predisposing behavioral characteristics, specifically externalizing tendencies. We had reason to believe that this might be the case, for there is evidence from the adult literature that the inheritance of substance dependence is in part mediated by the inheritance of personality (McGue et al., 1997, 1999). We further examined whether externalizing characteristics, in addition to predisposing to early use, may potentiate the environmental risk; that is, will an interaction be observed here as well'?

Once the predictive variance of the familial-risk variable was accounted for by the boys' externalizing traits, we biometrically modeled the relationships among temperament, environmental risk, and substance use. In so doing, we established whether externalizing tendencies and early-onset use do share genetic influences and, therefore, whether the vulnerability to use is transmitted in part via certain, heritable behavioral dispositions. In doing so, not only will we have provided evidence supporting the existence of a gene x environment interaction in the development of early-onset substance use, but also we will have gained insight into the mechanisms behind this interaction, into which inherited susceptibilities are interacting with environmental pressures to raise the likelihood of subsequent substance abuse.

METHOD

Participants

Our sample consisted of male twins who were born in the state of Minnesota and who participated in the Minnesota Twin Family Study (MTFS) during their early adolescent years. At the time of their first assessment, the twins ranged in age from 10 to 12 years, with an average age of 11 years, 9 months. When they returned for their follow-up assessment 3 years later, their average age was 14 years, 10 months. They are referred to in this paper as 11 and 14 year olds. Be-

cause follow-up data were not available for female twin participants at the time of our analyses, our sample is restricted to male twins.

The MTFS is a population-based, longitudinal study of twin adolescents and their parents. The families are broadly representative of the Minnesota population; approximately 98% are Caucasian. A complete description of the MTFS design and recruitment procedures is given by Iacono et al. (1999). That report also summarizes analyses showing that participants do not differ from nonparticipants in self-reported mental health but do differ slightly with respect to socioeconomic indicators. Specifically, participating fathers averaged 0.2 more years of education than nonparticipating fathers, and participating mothers averaged 0.3 more years of education than nonparticipating mothers. While these differences are statistically significant, they are quite modest in magnitude.

There were 664 males with substance-use data on both themselves and their parents. Our environmental-risk variable was a composite of five measures, and subjects were permitted to be missing no more than one of the five measures. This reduced our sample to 591. Of the 591, 549 also had temperament data. Missing data were the consequence of in-person interviews cut short by time limitations and subjects unwilling to finish by phone, self-report questionnaires that were neither completed at the time of the visit nor returned later by mail, and teachers not responding to requests for information about their students. The model-fitting analyses were based on the 244 twin pairs with both members having valid substance-use, environmental risk, temperament, and zygosity data and who comprised part of a twin-brother pair. This included 161 monozygotic (MZ) and 83 dizygotic (DZ) twin pairs. It should be noted that the excess of MZ twins does not necessarily reflect a recruitment bias because there was an overrepresentation of MZ twins in the population from which our sample was drawn (Hur et al., 1995), and the 488 individuals used in the model-fitting analyses were very similar to the unused 176 in their level of substance use [means and standard deviations were, respectively, 1.04 (1.37) and 1.04 (1.38); $p=.98$, two-tailed t test].

Zygosity Determination

Zygosity determination was based on the consensus of three separate estimates. Parents reported on physical resemblance, staff-evaluated physical similarity (facial appearance, hair and eye color, etc.), and an algorithm was used that makes use of ponderal and

cephalic indices and fingerprint ridge counts. In the event that the three estimates did not agree, a serological analysis was performed. An earlier validation study examined the serological results for 50 adolescent twin pairs whose three zygosity estimates had agreed. In every case, the serological analysis confirmed the agreement, suggesting that the MTFS's typical method of zygosity determination is highly accurate.

Measures

As part of the MTFS psychological assessment, the parents' and twins' substance use, the twins' psychosocial environments, and the twins' temperaments were assessed. These data were used to create the indices below.

Familial Risk Measured at Age 11

The boys' relative genetic risk was estimated from their biological parents' substance-related diagnoses. At the time of the boys' first assessment, a version of the Substance Abuse Module from the Composite International Diagnostic Interview (Robins et al., 1987) was used to interview their parents about present and past substance use. Approximately 98% of the twins' biological parents were interviewed in person; the rest were interviewed by phone. Questions addressed the parents' use of tobacco, alcohol, and illicit drugs.

After their visit, groups of two to four graduate students who had successfully completed an advanced-level course in descriptive psychopathology reviewed each participant's interview and assigned the appropriate diagnoses under the DSM-III-R system (American Psychiatric Association, 1987). Substance dependence diagnoses were categorized as "definite" if all criteria were met and "probable" if all but one necessary symptom were endorsed. Abuse diagnoses did not have this distinction. [See Iacono et al. (1999) and Elkins et al. (1997) for more comprehensive accounts of the MTFS diagnostic assessments.] Finally, the parents' self-reports were compared to their spouses' reports of their use. In the case that a self-report failed to acknowledge substance-related difficulties, but the spouse reported significant problems for that individual, the spouse's report was used to make the diagnosis.

Based on their parents' lifetime histories of substance diagnoses, the twins were placed in one of three risk groups. If either of the biological parents had been assigned a definite alcohol dependence diagnosis, then their children were placed in the high-risk group. To

be placed in the low-risk group, neither biological parent could have an alcohol abuse diagnosis or an alcohol dependence diagnosis at either the definite or the probable level. Furthermore, both parents had to be free of any definite or probable drug-related diagnoses. The remaining boys were placed in the intermediate-risk group. This middle group was thus comprised of boys whose parents had a definite or probable drug diagnosis but no alcohol diagnosis, a diagnosis of alcohol abuse, or a diagnosis of probable alcohol dependence.

Environmental Risk Measured at Age II

A global index of each boy's environmental risk was created by incorporating measures of strength of affiliation with deviant peers who may model or encourage substance use, as well as strength of association with social groups likely to discourage substance use. Specifically, this index incorporated the following five measures: Negative Peer Models, Attitude Toward School, Mother-Son Relationship, Religious Interests, and Extracurricular Activities. These variables were chosen because of their demonstrated link in past research to substance use. Peer influences not only are strong correlates of adolescent substance use (e.g., Patton, 1995) but may predict substance-use initiation (Kandel and Andrews, 1987; Sussman *et al.*, 1994). A high degree of commitment to school (Hawkins *et al.*, 1992), parental closeness (Williams and Smith, 1993), and parental involvement (Hundelby and Mercer, 1987), strong religious affiliations (Cochran, 1991), and participation in extracurricular activities (Kandel, 1982) are all fairly well established correlates of diminished risk for problematic substance use during adolescence.

Negative Peer Models. Up to three teachers per child reported on whether the child's group of friends could be characterized as tough and good fighters, dangerous to be with, rebellious, or a bad influence. On average, 1.42 teachers reported for each child, and their interrater agreement was 0.50. There were four items, each scored on a 5-point scale ranging from whether the boy's friends were in the lowest 5%, one of the middle thirds, or the top 5% of their class on that trait. The scale's internal-consistency reliability was 0.80. The four items were summed, and the average of the teachers' reports was used.

Attitude Toward School. Each twin's rearing mother (in 98.5% of cases also the biological mother) reported on her son's commitment or attachment to school by completing a seven-item questionnaire. Items were rated on a 4-point scale from definitely true to

definitely false and included assessment of the twins' interest and enjoyment of school and his motivation to earn good grades. Internal-consistency reliability was 0.83.

Mother-Son Relationship. Rearing mothers also reported on the level of conflict and the level of involvement with their sons. Included in this measure were items such as "My son and I often get into arguments" and "My son talks about his concerns and experiences with me." The conflict and involvement scales correlated -0.53 ($p < .001$) with each other. Each was comprised of 12 items and was rated on the same 4-point scale as above. The conflict scale's internal reliability was 0.88; the involvement scale's was 0.85. After the conflict scale was reversed, their scores were summed.

Religious Interests. Mothers further reported on the frequency with which their sons attended religious services or religious youth groups, read scripture, discussed religious teachings with their family, or celebrated holidays in a religious manner. Five items were used; the coefficient α for the scale was .80. Each item was answered on the same 4-point scale, and they were summed to create a total score.

Extracurricular Activities. The boys themselves reported in person on the degree to which they were involved in sports, music, or other organized after-school activities. Three questions were answered using a 4-point scale anchored at the extremes with "very involved" and "not at all involved." There was little correlation between the tendencies to be involved in sports, music, and other extracurricular activities, with the largest correlation between music and "other" ($r = .18$, $p < .001$); the α for the three items was .20. Because of these low intercorrelations, we developed one score to assess the degree of involvement (or lack of involvement) in the three types of activities. The boys were placed in one of five categories, ranging from individuals who were very involved in two or more activities to individuals who were not at all involved, or only marginally involved, in any activities.

For each measure, if the response to one item was missing, it was replaced with the average response for the other items. When more than one item response was missing, the measure was considered missing for that individual. All five measures were standardized so that each would be weighted equally regardless of variance, and then they were summed into one total score. If an individual was missing one of the five summed measures, it was replaced with the group mean; individuals missing more than one measure were excluded from the analyses.

Substance Use by Age 14

When they were 14, 90.9% of the boys completed in private a computer-administered, self-report of their substance use. The remaining 9.1% were asked similar questions in a telephone interview. Each twin's score on this measure was simply a summation of the number of classes of substances he had tried from the following list of 11: tobacco, alcohol without parents' permission, marijuana, amphetamines, tranquilizers, Quaaludes, inhalants, cocaine, PCP or psychedelics, heroin, and steroids. The coefficient α for this scale was .68. Two substance-bleomycins and cadrines (one a nonpsychoactive prescription drug and the other fictitious)-were also questioned about and were used as validity items. Those boys who endorsed using these substances were excluded. Prior to all analyses, this measure was log transformed [$\log(\text{raw score} + 1)$] to reduce its positive skew.

Temperament Assessed at Age 11

Teacher ratings of inattention, oppositionality, and hyperactivity were combined to create a 40-item measure of externalizing tendencies. The individual components that went into externalizing have α 's of .96 (inattention), .96 (oppositionality), and .92 (hyperactivity). Reports were used from up to three teachers per child (on average, 1.42 per child). The average interrater agreement was 0.75. Each boy's score was the mean of his teachers' responses. This measure was also log transformed prior to analyses to reduce its positive skew.

Analysis

Twin study methodology was employed for the univariate and Cholesky decomposition structural-equation modeling. Twin methodology uses the difference in the proportion of shared genes between MZ and DZ twins to estimate the contributions of genetic and environmental factors to observed behaviors or characteristics (i.e., phenotypes). MZ twins share all of their genes, while DZ twins share on average 50% of their segregating genes. If one assumes that MZ and DZ twins are equally apt to share environmental factors that are etiologically relevant for the trait in question [see Kendler (1993) for a defense of this assumption], the MZ twin correlation is expected to be greater than the DZ twin correlation for any genetically influenced trait. Following this logic, the twin design estimates the proportion of genetic influence on a trait (and, alternatively, the proportion of environmental influence)

from the difference between the MZ and the DZ twin correlations.

The phenotypic variance of each trait was decomposed into variance due to additive genetic effects (a^2), shared environmental effects (c^2), and nonshared environmental effects plus measurement error (e^2). Shared environmental effects lead to similarities between children reared in the same family, while nonshared environmental effects are experiences unique to each individual and thus create differences between children of the same family. Under the assumption that genetic and environmental factors combine independently and additively, the total phenotypic variance for a trait is the sum of $a^2 + c^2 + e^2$. [Interested readers are referred to Plomin *et al.* (1997) for an explication of twin study methodology.]

Both univariate and Cholesky decomposition model-fitting analyses were conducted. Univariate analyses allowed us to decompose the variance of temperament and environmental risk as measured at age 11, and substance use as measured at age 14, into proportions due to genetic and environmental factors. The Cholesky decomposition then permitted an examination of the extent to which each type of influence contributes to the covariances of the three measures.

Mx, a structural-equation modeling program developed by Neale (1997), was used to complete the model-fitting analyses. Mx uses maximum-likelihood model-fitting techniques to fit models to covariance matrices. This method maximizes the fit between the model and the data and in this way determines which parameter estimates provide the smallest discrepancies with the data. In the following results, the chi-square statistic represents a goodness-of-fit index, with statistically significant chi-square values associated with a relatively poor model fit. Improvements in the model's fit, from adding or omitting parameters, can be assessed by noting the change in chi-square. Akaike's (1987) information criterion (AIC), which is calculated from the model's chi-square minus twice its degrees of freedom, also offers a measure of model fit and is conventionally used to determine the best-fitting models. The AIC statistic considers goodness of fit while penalizing overparameterization, and the model with the lowest AIC value is generally considered best.

RESULTS**Age 14 Substance Use**

Although the use of 11 substances was queried, the maximum number used by any one 14 year old was

9. Table I indicates the percentage of boys who had ever tried each class of substance by age 14, without regard to the quantity or frequency of their use. The modal number of classes of substances initiated was 0, the mean 1.00, and the standard deviation (SD) 1.35.

The proportion of 14 year olds within our sample that had tried various classes of substances did not differ remarkably from national norms. According to a 1996 nationwide survey, 37.2% of American males between 12 and 17 years of age have tried a cigarette (Substance Abuse and Mental Health Services Administration, 1998). The MTFSS assessment asks about all forms of tobacco, not just cigarettes, and this may explain our slightly higher estimate of 40.61% by age 14. The national survey reported that 38.3% of males aged 12 to 17 have used alcohol at some point in their life. In our sample, 33.83% reported having tried alcohol without their parents' permission. For the national statistics of illicit drug use, males and females were grouped together and alcohol was included as a drug. Of those aged 12 to 17, nationally, 7.6% have tried alcohol and marijuana but no other illicit substances; 8.1% have tried three illicit substances, one of which could have been alcohol. How the national statistics were reported makes a direct comparison to our data in Table I difficult, but the numbers do suggest that marijuana use by our sample may be slightly higher than the national norm.

The Effect of Familial and Environmental Risk

We examined the data for main effects and for an interaction between our familial- and environmental-risk variables in the prediction of substance use. SPSS 7.5 (SPSS, Inc., 1997) was used to carry out the regression analyses. The dependent variable was the log-transformed tally of the number of classes of substances each boy had tried by age 14. The independent variables were the familial-risk variable, the global environmental-risk index, and a product to capture their interaction. The independent variables, prior to regression analyses, were standardized to reduce the correlation between themselves and their product. Table II presents the mean value for each measure, including substance use, according to familial risk group. See Table III for the intercorrelations of the measures.

Individuals for whom one of the five environmental-risk measures had been missing and thus supplemented with the group mean of that measure ($n = 169$) did not differ from those not missing any responses in the number of substances they had tried (two-tailed t test). They differed only in their attitude toward school,

Table I. Percentage Who Had Tried Each Class of Substance by Age 14

Substance	Percentage
Tobacco	40.61
Alcohol	33.84
Marijuana	13.37
Amphetamines	3.05
Tranquilizers	0.68
Quaaludes	0.68
Inhalants	4.57
Cocaine	0.85
PCP or psychedelics	1.69
Heroin or opiates	0.17
Steroids	0.34

being approximately 0.35 SD ($p < .005$) lower on that measure. No other significant differences were noted.

Regression results indicated that both familial risk ($p < .005$) and environmental risk ($p < .001$) independently predicted substance use. Furthermore, the interaction of the two risk factors resulted in greater likelihood of early-onset substance use than did either alone or both in additive combination ($p < .01$ for the interaction term). The multiple correlation was 0.32 [$F(3,587) = 21.81, p < .001$]. Figure 1 displays the regression equations for the low, intermediate, and high familial-risk groups. The y axis is the log-transformed substance use variable; therefore, for example, 0 corresponds to no substance use and 0.6 corresponds to the use of three classes of substances. In this graph, low environmental risk corresponds to a relatively large number of prosocial affiliations, and high environmental risk to a lack of prosocial affiliations. As Fig. 1 illustrates, familial risk is most predictive among those with a high level of environmental vulnerability.

The Contribution of Temperament

During the second stage of analysis, we investigated the role of temperament in the prediction of early-onset substance use. Specifically, can externalizing tendencies account for the predictive variance of our familial-risk measure? That is, is the inherited predisposition to substance use embodied in individual differences in externalizing tendencies?

We used hierarchical regression methods to answer this question. We first entered temperament, environmental risk, and their interaction into a regression equation predicting age 14 substance use. In the second step, we added the familial-risk variable to determine

Table II. Externalizing Characteristics, Environmental Risk, and Number of Substances Used by Age 14, by Familial Risk Group

Measure	Familial risk group						ANOVA results	
	Low		Intermediate		High		F(df)	p
	M	SD	M	SD	M	SD		
Externalizing, characteristics (i.e., temperament)	55.17 ^a (n = 178)	16.29	61.66 ^b (n = 141)	22.04	65.99 ^b (n = 230)	24.58	12.97(2,546)	<.001
Environmental risk	-0.47 ^a (n = 198)	2.48	-0.34 ^a (n = 146)	2.46	0.44 ^b (n = 247)	2.88	7.73(2,588)	<.001
No. of substances used by 14	0.67 ^a (n = 198)	0.91	1.03 ^b (n = 146)	1.35	1.24 ^b (n = 247)	1.57	7.19(2,588)	<.005

Note.^{a,b}According to post hoc Student-Newman-Keuls analyses, means marked with distinct superscripts differ significantly from each other. The externalizing and substance-use means are presented prior to the scales having been log-transformed, but the ANOVA results are based on the log-transformed scores.

Table III. Intercorrelations of Measures

	Measure			
	Familial Risk (F ₁₁)	Temperament (T ₁₁)	Environmental risk (E ₁₁)	Substance use (SU ₁₄)
F ₁₁	—			
T ₁₁	0.21	—		
E ₁₁	0.15	0.55	—	
SU ₁₄	0.15	0.32	0.28	—

Note. All correlations are significant (p < .001).

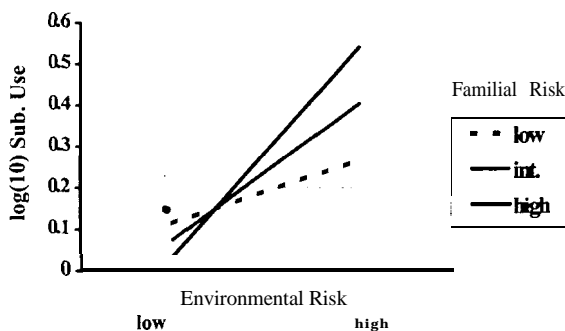


Fig. 1. Substance use for three levels of familial risk

whether, once temperamental factors had been taken into account, familial risk still predicted use. In the first step, externalizing tendencies ($p < .001$), environmental risk ($p < .005$), and their interaction ($p < .05$) all emerged as statistically significant. When entered at the second step, familial risk added only 0.01 to the multiple correlation and was no longer significantly predictive of age 14 substance use [$F(2,543) = 2.44, p > .05$]. Thus, the familial-risk variable could apparently be re-

placed by a more proximal measure of genetic risk: externalizing tendencies.

However, unlike the original interaction, this one appeared to be driven by a small group of boys whose product terms were extreme. After eliminating 12 individuals who were more than 3 SD from the mean on the temperament x environmental risk interaction term, the interaction was no longer significant ($p = .43$), although the other independent variables remained significant ($p < .001$ for externalizing and $p < .05$ for environmental risk). It therefore appears that any interaction between temperament and environmental risk fails to apply to the majority of individuals.

Univariate and Multivariate Twin Analyses

There were no significant differences between the means of the MZ and DZ twins (two-tailed t tests) on the temperament, environmental-risk, or substance-use variables. Levene's test for homogeneity of variance further revealed no significant differences between the MZ and the DZ score variances. This provides support for the equal-environments assumption inherent in our

model fitting because, if greater similarity of MZs' than DZs' environments had influenced the traits in question, we should have seen trait variance differences between the two zygositys.

Intraclass twin correlations were calculated to provide a preliminary estimate of the extent to which genetic and environmental factors influence the three variables of externalizing tendencies, environmental risk, and substance use (see Table IV). All correlations differed significantly from zero ($p < .001$), and for all three variables the MZ correlation was significantly larger than the corresponding DZ correlation [$\chi^2(1)=8.02$, $p < .005$, for externalizing characteristics as measured at age 11; $\chi^2(1)=13.16$, $p < .005$, for environmental risk as measured at age 11; and $\chi^2(1)=7.03$, $p < .01$, for substance use as measured at age 14]. Whenever the DZ correlation exceeds half the MZ correlation, as it clearly does here for all measures, shared environmental influences are implied.

Univariate model fitting suggested that the full ACE model fit best for all three variables. Genetic and shared environmental influences each accounted for between 30 and 50% of the variances. No parameter— u^2 , c^2 , or e^2 —could be dropped from any of the measures without significantly compromising fit. See Table IV for the precise parameter estimates and associated confidence intervals.

Cholesky Decomposition

After fitting the univariate models, we used a Cholesky decomposition model to explore the amount of genetic and shared environmental variance that is common to the three variables. Figure 2 depicts the ACE Cholesky model. This model contains genetic and environmental factors that substance use shares with temperament (A1, C1, and E1), and the environmental risk variable net temperament (A2, C2, E2), as well as genetic and environmental factors that contribute uniquely or residually to substance use (A3, C3, and E3).

The full Cholesky model, in which all parameters were estimated, adequately fit the data [$\chi^2(24)=18.55$, $p = .78$, AIC ≈ -29.45]. In Table V, the genetic and environmental variance of each variable within the full model is decomposed into that which is attributable to influences that are shared with previous variables and that that is unique or residual to that variable. Confidence intervals at the 95% level are also given.

Because we were most interested in the prediction of substance use, we determined which aspects of its variance were statistically different from zero (and thus

which factors contributed significantly). As is apparent from the last line in Table V, the common shared environmental variance of 20% was significant, as was the unique or residual 39% of genetic variance and 26% of nonshared environmental variance. The remaining contributing variances to substance use were not significantly different from zero, as they could be dropped from the model without compromising fit. The attributable genetic influence (i.e., a_{31} and a_{32}) could be dropped ($\Delta\chi^2=.85$, $\Delta df=2$, ns), as could the attributable nonshared environmental variance ($e_{31}=e_{32}=0$; $\Delta\chi^2=5.55$, $\Delta df=2$, ns), as could the shared environmental variance that was unique to substance use ($c_{33}=0$; $\Delta\chi^2=.37$, $\Delta df=1$, ns). In summary, the predictive relationship between our measures of temperament, environmental risk, and subsequent substance use does not appear to be explained by shared genetic factors. Rather, it seems to be explained by those shared environmental factors that are common to all three variables. However, the large confidence intervals given in Table V preclude the drawing of any firm conclusions.

DISCUSSION

This paper's primary goal was to examine interactive effects between genetic and environmental influences in the genesis of early-onset substance use. Our sample consisted of 591 males from the youngest MTF cohort. The boys' relative genetic or familial risk was inferred from their parents' substance-related diagnoses. A global index of the boys' environmental risk aggregated measures of their associations with deviant peers, who are liable to promote substance use, as well as their affiliations with academic, familial, religious, and community groups, which typically discourage substance use. Both risk measures were derived from information gathered when the boys were age 11. We then looked for interactive effects in the prediction of early-onset substance use, which was operationalized as the number of classes of substances tried by age 14.

Our results indicate that the number of substances used by age 14 varies as a function of the boys' standing on both the familial- and the environmental-risk measures; each independently and significantly predicted substance use. Their interaction was also significant. Individuals whose familial and environmental risks were estimated to be high at age 11 had tried substantially more substances by age 14 than would have been expected from a simple summation of their relative risks.

Table IV. Parameter Estimates for the Temperament, Environmental-Risk, and Substance-Use Measures

Variable	Intraclass twin correlation		Best-fitting model						
	MZ	DZ	Parameter estimate (and 95% CI)			Fit			
			a^2	c^2	e^2	χ^2	df	p	AIC
Temperament	0.77	0.56	0.39 (0.11-0.721)	0.37 (0.05, 0.60)	0.24 (0.19, 0.31)	.08	3	.99	-5.92
Environmental risk	0.84	0.63	0.35 (0.16, 0.61)	0.48 (0.21, 0.66)	0.17 (0.13, 0.22)	1.02	3	.80	-4.98
Substance use	0.72	0.51	0.41 (0.15, 0.7-t)	0.31 (0.00, 0.55)	0.28 (0.22, 0.35)	.66	3	.88	-5.3-t

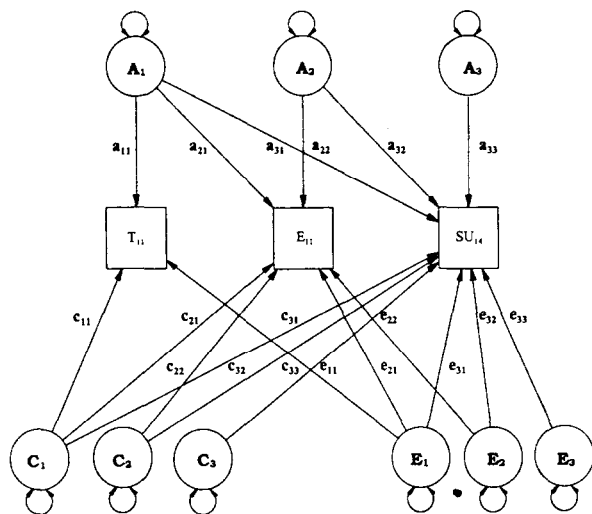


Fig. 2. Cholesky decomposition model examining the common Genetic (A), shared environmental (C), and nonshared environmental influences (E) between personality and environmental risk as measured at age 11 and substance use by age 14. The observed variables (in squares) are temperament assessed at age 11 (T_{11}), environmental risk assessed at age 11 (E_{11}), and substance used assessed at age 14 (SU_{14}). The diagram is shown for one twin only. When drawn for both twins, correlational arrows with values of 1.0 link the shared environmental variables of twin A with twin B. The genetic variables correlate 1.0 for MZ twins and 0.5 for DZ twins. Unique environmental influences are uncorrelated.

Environmental influences may alter the consequences of genetic risk, and genetic factors are capable of modifying a child's responsiveness to his environment. As Fig. 1 illustrates, when a boy's environmental risk is low-he experiences positive peer influences, enjoys school, is close to and gets along well with his mother, participates in a religious community, and partakes in other extracurricular activities-his level of ge-

netic or familial risk is largely irrelevant to determining his substance use. Low environmental risk thus seems to play a protective role, buffering against potentially deleterious effects of high familial risk. On the other hand, when the environmental risk is high, familial risk becomes consequential. When boys associate with deviant peers, are not strongly attached to prosocial groups, and also have a family history of alcoholism, they tend toward a precocious initiation into substance use. Their level of use by age 14 is significantly higher than that of boys with the same environmental risks whose parents have always been free of substance-related diagnoses.

As previously mentioned, these data should not be interpreted as unequivocal evidence in favor of a gene x environment interaction in the initiation of substance use; any conclusions regarding interactive effects must be tempered with reservations. Nonetheless, our results are consistent with such an interpretation. And despite any qualifications, it is certainly intriguing to find evidence in favor of an interactive effect, for conceptually it seems highly probable that early adolescent substance use emerges out of an interplay between inherited tendencies and environmental circumstances.

At the same time that we favor a cautious but hypothesis-supporting interpretation of the data, we acknowledge divergent interpretations. The boys' relative levels of genetic risk were inferred from parental diagnoses. Even assuming perfect diagnostic validity, not all children of alcoholic parents will have inherited the appropriate quantity or configuration of genes to put them at high risk. With reference to Fig. 1, it is possible that what we have called low environmental risk is not a protective factor, but merely a marker for a group of children who do not have the heritable disposition toward substance use. Regardless of parental di-

Table V. Sources of Variance for the Full Cholesky Model

Scale	Proportion of variance (and 95% CI)					
	Attributable to A1, C1, E1			Residual		
	Genetic	Shared E	Nonshared E	Genetic	Shared E	Nonshared E
Temperament	0.39 (0.14, 0.70)	0.37 (0.07, 0.60)	0.23 (0.18, 0.31)			
Environmental risk	0.14 (0.01, 0.40)	0.19 (0.01, 0.54)	0.01 (0.00, 0.03)	0.22 (0.03, 0.44)	0.29 (0.00, 0.47)	0.15 (0.12, 0.20)
	Attributable to A1, C1, E1 and A2, C2, E2					
Substance use	0.03 (0.00, 0.52)	0.20* (0.02, 0.50)	0.01 (0.00, 0.03)	0.39* (0.00, 0.64)	0.11 (0.00, 0.40)	0.26* (0.20, 0.33)

Note. Those proportions of variance of the substance-use measure that differ significantly from zero are marked with an asterisk.

agnoses, these boys may *not* have inherited those characteristics that would make it likely that they would experience an early initiation into substance use, and this same character structure may have facilitated bonding to prosocial groups. Other children also at low genetic risk may have scored high on the environmental-risk measure because they are isolated and generally uninvolved in their social surroundings, not because they tend toward antisocial activities.

Interestingly, if one follows this interpretation, there are still effects of genetic risk at the high end of the environmental-risk continuum. Individuals at intermediate and high genetic risk who fail to affiliate with prosocial groups will experience a more negative outcome than individuals at low genetic risk with the same affiliative patterns. Therefore, one may equivocate on the interpretation of the interactive effects, but the data do suggest that within the same high-risk environment, higher familial risk is associated with more substance use by age 14.

A secondary goal was to investigate the role that temperament plays in the above results. We determined that the majority of the familial-risk measure's predictive variance could be accounted for by the boys' temperaments as measured at age 11, specifically their externalizing tendencies. This provided preliminary support for our hypothesis that much of the risk for substance use is transmitted genetically from parent to child via certain personality or temperamental characteristics.

There would have been a number of advantages to replacing the familial-risk variable with a measure of externalizing tendencies. For one, in using parental substance-use diagnoses (i.e., phenotypes) to estimate chil-

dren's genetic risk (i.e., genotypes), we were using an indicator that was two steps removed from what we truly hoped to be assessing. The boys' temperaments could potentially offer a more direct appraisal of their inherited risks. Additionally, by inferring risk from the parents' diagnoses, we were forced to assume that both children, even DZ twins, had equivalent levels of heritable risk. Using externalizing traits, we could more accurately assess each individual child's risk.

Unfortunately, while our initial results did suggest that the heritable risk for substance use might take the form of temperament, the model fitting did not corroborate this conclusion. While a substantial proportion of early substance use's variance is attributable to additive genetic effects (approximately 41%), only a very small and nonsignificant proportion of its variance is attributable to genetic influences that it shares with temperament and environmental risk (3%; see Table V). Rather, approximately 20% of the variance in the early use of multiple substances originates in shared environmental factors that are common to externalizing and environmental risk. Parents and other between-family factors are influencing both temperament and substance use and contributing to their correlation; however, these familial influences are not genetic in origin.

These modeling results are unexpected. One possible explanation is that the boys' young age accounts for the strong influence of shared environmental factors. Some previous research has suggested that shared environmental influences on substance use are more prominent than genetic influences during mid adolescence but that the situation reverses as individuals move into adulthood (e.g., Koopmans and Boomsma, 1995). As the boys

age. the proportion of variance of both temperament and substance use that is attributable to genetic influences is apt to increase. Then, perhaps shared genetic variance would be detected. It is also possible that a replication study would draw different conclusions, as the confidence intervals on our model fitting are quite large and hence precluded the drawing of any firm conclusions.

We had further theorized that an interaction might also emerge between temperament and environmental risk. Although an interaction was observed for the entire sample, on closer inspection it became clear that it was driven by a small group of boys whose product terms were extreme. Any multiplicative influence of externalizing tendencies upon environmental risk failed to apply to the majority of individuals. Temperament may capture the predictive variance of our familial-risk variable, but it does not capture the interaction with environmental risk.

In summary, this report provides evidence consistent with the existence of a gene x environment interaction in the etiology of early-onset substance use. Low levels of environmental risk seem to mitigate the effects of inherited vulnerabilities, while high levels of environmental risk augment these same effects. The predictive variance of our genetic- or familial-risk variable could be accounted for by a measure of externalizing characteristics. Yet it was not a genetic transmission of these characteristics that was putting the sons of alcoholics at high risk for an early initiation into substance use. The predictive relationship between temperament at age 11 and substance use by age 14 seems to be due to common shared environmental—not genetic—factors. The latter results must be qualified by large confidence intervals. Nonetheless, they stress the potential value of identifying those shared environmental conditions that underlie the association of externalizing and affiliative tendencies with subsequent substance use, for they may be excellent targets for prevention efforts.

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