Genetic and Environmental Effects on Offspring Alcoholism

New Insights Using an Offspring-of-Twins Design

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Context: Although there is now considerable evidence that genetic effects play a critical role in the development of alcohol dependence (AD), theoretical and methodological limitations of this literature require caution in describing the etiology and development of this disorder.

Objective: To disentangle genetic and environmental effects on AD by means of the infrequently used, yet potentially powerful, offspring-of-twins design.

Design: Offspring of twins.

Participants: Male monozygotic and dizygotic twins concordant or discordant for AD and control pairs from the Vietnam Era Twin Registry were assessed, as were the offspring of these twins and the mothers of these offspring.

Interventions: Structured psychiatric interviews.

Main Outcome Measures: Participants' psychiatric, alcohol abuse (AA), and AD histories (*DSM-IV*).

Results: Offspring of monozygotic and dizygotic twins with a history of AD were significantly more likely to exhibit AA or AD than were offspring of nonalcoholic fathers. Offspring of an alcohol-abusing monozygotic twin whose co-twin was AD were also more likely to exhibit AD than were offspring of nonalcoholic twins. In contrast, offspring of an unaffected (ie, no history of abuse or dependence) monozygotic twin whose co-twin was AD were no more likely to exhibit AA or AD than were offspring of nonalcoholic twins.

Conclusions: These findings support the hypothesis that family environmental effects do make a difference in accounting for offspring outcomes, in particular, that a low-risk environment (ie, the absence of parental alcoholism) can moderate the impact of high genetic risk regarding offspring for the development of alcohol-use disorders.

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THE AIM of the present project is to examine the impact of genetic and environmental factors on alcoholism through use of the infrequently used, but potentially powerful, offspring-of-twins design. In so doing, our intent is to better appreciate the relative effect of the alcoholic family environment in elevating alcoholism risk beyond that associated with genetic risk for the disorder.

FAMILY STUDIES OF ALCOHOLISM

That children of alcoholics (COAs) may be at increased risk for alcoholism, other psychiatric disorders, and general psychological and interpersonal impairments has been discussed in the clinical and scientific literature for many decades.[1-5] Much of the extant work in this area has been conducted by 2 relatively nonoverlapping research traditions with distinct strengths and limitations.[1,6-10]

The psychosocial research tradition has (1) developed increasingly sophisticated models of etiology, (2) defined a variety of key mediator and moderator mechanisms that may account for or qualify the impact of family history risk on offspring outcome, and (3) produced several high-quality, longitudinal data sets aimed at testing alternative models of mediation and moderation.[11-15] The major shortcoming of this line of research is one of ambiguity of findings, since all such efforts have involved simple family studies so that separation of family genes from family environments has not been possible. In contrast, behavioral genetic studies have offered an increasingly persuasive argument that genetic effects ultimately account for 40% to 60% of the variance in alcohol dependence (AD) risk and that the remaining variance is only

partly explainable in terms of shared family environmental effects.[9,16] The strength of these conclusions, however, must be tempered by several substantial limitations.[6] Most important, little is known about how genetic effects are mediated and moderated by environmental effects, that is, the nature of gene-environment correlations and gene-environment interactions relevant to the etiology and course of alcoholism. Failure to assess pertinent shared environmental risk factors may be especially problematic for studies of genotype × shared environment interaction effects, since in the classical twin design these interaction effects, unless explicitly modeled, will be confounded with the genetic main effect.[17]

THE NEED FOR ALTERNATIVE GENETIC DESIGNS

Of the various research designs that have been used in family studies of AD, each is characterized by strengths and limitations[6]: (1) the family study method does not permit resolution of genetic and environmental causes of parent-offspring resemblance; (2) the classical twin design confounds estimates of genetic effects and genotype × shared environment interaction effects; (3) the adoption design studies a limited number of individuals raised in high-risk environments, since adoptive parents are typically older, of higher socioeconomic class, unusually motivated to provide a nurturing environment for their adoptive child, and, at least by self-selection (if not by agency screening), unlikely to exhibit a wide range of characteristics that could have an important impact on the child's development[18]; and (4) the twins-reared-apart design is another potentially powerful method, although most of these results are mainly informative about consumption rather than AD.[19]

The offspring-of-twins design[20] has been used less often in behavioral genetic studies of psychiatric disorders, and, to our knowledge, never in a rigorous assessment of AD etiology. This approach provides a powerful pseudoadoption design[21,22] in which genetic and environmental risk status can be inferred from the co-twin's history of alcoholism. Most important, children raised by an alcoholic monozygotic (MZ) or dizygotic (DZ) twin parent are at high risk for psychiatric disorders and other health problems because of high genetic risk and high environmental risk. In contrast, children raised by the nonalcoholic twin of an alcoholic MZ co-twin are at low environmental risk because these children have not grown up in an alcoholic home, but they are at the same (high) genetic risk as the children raised by an alcoholic twin because the fathers have identical genotypes. In turn, children raised by the nonalcoholic twin of an alcoholic DZ co-twin are also at reduced (low) environmental risk but at only intermediate genetic risk because DZ twin pairs on average share only half of their genes.[6]

Given these differences in risk profile, the child of an alcoholic parent should be no more likely to develop alcoholism than the child of a nonalcoholic parent who is an MZ co-twin of an alcoholic individual in the absence of any environmental effect of parental AD. On the other hand, excess rates of alcoholism in the former group, after controlling for psychiatric disorders and assortative mating, would imply an environmental impact of parental alcoholism. The addition of DZ twin pairs and their spouses and offspring is critical for clarifying interpretations of findings; that is, without this group, equally elevated rates of alcoholism in the offspring of alcoholics and of nonalcoholic MZ co-twins of alcoholics could be explained by either genetic transmission or environmental effects of a risk factor for which the twin pairs were perfectly correlated (eg, religious affiliation). Further discussion of these various genetic designs can be found in several sources.[6,23]

The present study assessed male MZ and DZ twins concordant or discordant for AD or concordant for no AD and their biological offspring and the biological mothers of their offspring. Three major hypotheses guided our analyses:

1. The prevalence of offspring alcohol abuse (AA) and AD will be highest for the biological children of an alcoholic parent (ie, alcoholic fathers from either MZ or DZ pairs) and lowest when fathers exhibit no AD and have no elevated genetic risk for the disorder (ie, father's co-twin is nonalcoholic). This hypothesis is based on a sizeable literature indicating that COAs exhibit higher rates of alcohol-use disorders than do non-COAs.[2]

2. In the absence of paternal AD, offspring with elevated genetic risk (ie, where the unaffected father's MZ or DZ co-twin is alcoholic) will exhibit lower rates of AD than will COAs. Differences in rates of offspring alcoholism will be greater between COAs and children of their unaffected DZ twins than between COAs and children of their unaffected MZ twins given the lower genetic loading in the former vs the latter. This expectation is based on the contention that the environment associated with parental alcoholism—not just parental genes—affects offspring development (albeit perhaps in interaction with multiple offspring genetic vulnerability) through impact on family stability, parenting practices, and sibling relationships; modeling effects; and general socioeconomic status.[3,5,7,24-26] Finally, differences between COAs and offspring of control MZ and DZ twins (from concordant unaffected twins) would be explained in terms of differences in genetic and environmental risk.

3. To the extent that AA and AD represent different points along the same continuum of risk, as suggested by several studies[27-29] using latent class analysis, the impact of no parental alcohol problems, parental AA, and parental AD will result in different risk profiles for offspring. In particular, a child with high genetic risk (because the father's MZ co-twin is AD) is not necessarily at low environmental risk if his or her father exhibits AA but not AD.

METHODS

PARTICIPANTS

Data for classifying twins were derived from interviews performed in 1992 with members of the Vietnam Era Twin Registry.[30] The Registry is composed of male-male twin pairs born between January 1, 1939, and December 31, 1957, who served in the US military between May 1, 1965, and August 31, 1975.[3,31]

In 1987, twins completed a mailed questionnaire of general health[32] from which data on their biological offspring, including sex and age, were obtained. In 1992, Registry members were administered a telephone psychiatric diagnostic interview covering a range of disorders, including alcohol and drug dependence.[33] Twin pairs were selected based on the following criteria: (1) completed the 1987 and 1992 surveys, (2) reported having children born between 1974 and 1988, and (3) identified as concordant or discordant for a lifetime diagnosis of *DSM-III-R*[34] AD or as a member of a random sample of non-AD control pairs. We targeted a sample of 1464 twins (732 pairs), their children, and the children's mothers.

Terms of the human subjects approval from the institutional review boards of the participating institutions required that the twin be contacted first to obtain permission to contact mothers and children. Then, the mothers were contacted for participation and for permission to contact the children, so that, ultimately, child participation required contact of and permission from both parents. Of the eligible twins, 1213 (83%) participated in the telephone interview. Participating twins identified and gave consent to contact 1070 mothers, of whom 862 (81%) participated in the telephone interview. Consent from both parents to contact their children was obtained for 1487 offspring. Of these, 1270 (85%) participated in the telephone interview. The nonparticipating twins, mothers, and offspring were deceased, unable to be located, or unavailable, or they refused to take part in the study. To assess for potential sample bias and impact on generalizability of findings, we developed and tested a model of offspring response as a function of parental and offspring characteristics. Results indicated that (1) the alcoholism status of the father was not a significant predictor of offspring participation, (2) only offspring sex was associated with refusal to participate (males less likely than females), (3) sampling weights derived from paternal sociodemographic variables could recapture the distribution of key variables in the target population, and (4) nonresponse bias was minimal.

ASSESSMENT

Computer-assisted telephone interviews were conducted by trained interviewers from the Institute for Survey Research, Temple University, Philadelphia, Pa. Offspring were administered a modified telephone version of the Semi-Structured Assessment for the Genetics of Alcoholism interview[35] that permitted determination of *DSM-IV*[36] lifetime and current diagnoses of AA, AD, major depression, childhood conduct disorder, oppositional defiant disorder, anxiety disorders (including social phobia, panic with and without agoraphobia, and generalized anxiety disorders), nicotine dependence, cannabis dependence, and abuse of 7 classes of drugs. In addition, nondiagnostic sections—including suicidality; traumatic events; extensive drug-, tobacco-, and alcohol-use histories; and sexual maturation—were covered. The present study focuses on offspring AA and AD as the outcomes of interest. The maternal interview, also administered in computer-assisted telephone interview format, covered her own *DSM-IV* history of AA, AD, and major depression and included screens for drug use, nicotine dependence, mania, antisocial personality, and her use of substances for each of her pregnancies with the children. Mothers were also asked about their children's behavior, including attention-deficit/hyperactivity disorder, conduct, major depression, alcohol use, and various nondiagnostic sections on rearing history and family background. For the twin fathers, extensive psychiatric histories had been obtained in 1992 during their participation in the Harvard Drug Study, so that the assessment for the present study included a short interview covering primarily their alcohol-use and problems history, using an adaptation of the Lifetime Drinking History.[37]

DATA ANALYSIS

For primary analyses, we used a 6-group classification scheme based on the AA and AD histories of the twin parent and the parent's co-twin: group 1 consisted of a twin father (whether MZ or DZ) with a history of AD and an MZ or DZ co-twin with any or no diagnosis; group 2, a twin father with AA and an AD MZ co-twin; group 3, an unaffected twin father (no history of AA or AD) and an AD MZ co-twin; group 4, a twin father with AA and an AD DZ co-twin; group 5, an unaffected twin father and an AD DZ co-twin; and group 6, both twins, whether from MZ or DZ pairs, unaffected. Covariates included maternal AD, AA, and depression; paternal depression, antisocial personality disorder or conduct disorder, and illicit drug abuse or dependence; marital status (ever divorced); paternal educational and employment status; and offspring age and sex. In initial descriptive analyses, we tested for sociodemographic differences as a function of the 6 risk groups, using linear or logistic regression models to predict each sociodemographic outcome measure as a function of 5 dummy variables corresponding to the risk groups and using group 6 controls as the comparison group. We then estimated a polytomous logistic regression model to jointly model the risk of (1) AD and (2) AA, relative to no alcohol diagnosis, as a function of the same 5 dummy variables and relevant control variables. Odds ratios and their 95% confidence intervals are reported for these analyses, estimated using the Huber-White robust variance option to correct for observations on multiple individuals from the same family (full or half siblings from the same father or cousins related through the father and the father's co-twin).[38]

A critical assumption underlying our use of a classification with 6 risk groups is that the same familial factors (genetic or shared environmental) that determine risk of AD also determine risk of AA in those who are not dependent on alcohol. To test this hypothesis, a standard bivariate genetic model[39,40] was fitted to data from the entire Harvard Twin Study sample on (1) number of *DSM-III-R* AD symptoms and (2) history of *DSM-III-R* AA (defined as a binary variable but set to missing if a twin met the criteria for AD). Model fitting was conducted by the method of maximum likelihood using a quadrivariate normal multiple threshold model using the MX statistical program[40] (see Heath and Nelson[41] for technical details of this approach). Results indicated that neither the genetic correlation nor the shared environmental correlation between AA and AD differed significantly from unity ($P > .05$). These results validated our 6-group classification scheme.

<div style="text-align:center">**RESULTS**</div>

SAMPLE CHARACTERISTICS

There were approximately 1.8 siblings per family; twin fathers and mothers averaged 50 and 47 years of age, respectively; more than 50% of fathers had greater than a high school education, and 90% were employed full time at the time of the study; and offspring (approximately 52% male) ranged in age from 12 to 26 years (SD=4.0 years) (**Table 1**). Although there were no significant cross-group differences in these family characteristics, paternal education (as expected) differentiated AD from non-AD fathers ($t_{1,681}$, $P < .001$) and AD twins from their nonaffected co-twins within AD discordant pairs ($t_{1,104}$, $P < .01$).

Table 1. Sociodemographic Characteristics of All Participants by Paternal Alcoholism Status

Characteristic	AD, MZ, and DZ Twins (n = 587)	MZ Twin With Abuse; Co-twin With AD (n = 68)	MZ Twin Unaffected; Co-twin With AD (n = 94)	DZ Twin With Abuse; Co-twin With AD (n = 67)	DZ Twin Unaffected; Co-twin With AD (n = 91)	MZ and DZ Unaffected Control Twins (n = 276)*
Siblings, mean (SD), No.	1.73 (1.03)	1.63 (1.01)	2.05 (1.23)	1.93 (0.86)	1.94 (1.42)	1.71 (1.00)
Child age, mean (SD), y	19.6 (4.1)	19.4 (3.8)	19.6 (4.1)	18.7 (4.0)	18.8 (3.8)	19.6 (4.0)
Paternal age, mean (SD), y	50.34 (2.60)	50.57 (2.20)	50.97 (2.78)	50.43 (2.43)	50.23 (2.51)	50.95 (2.54)
Maternal age, mean (SD), y	47.37 (3.82)	47.76 (3.69)	47.39 (4.34)	46.98 (3.72)	47.17 (3.64)	48.31 (3.60)
Male offspring, %	48.9	47.1	53.2	50.7	50.5	43.5
Father employed full time, %	95.0	89.4	90.4	97.0	93.4	97.1
Father graduated from high school, %	57.4	58.8	64.9	67.12	69.2	65.2
Mother graduated from high school, %	69.2	72.7	59.8	79.4	63.2	73.8
Parental marital status: divorced, %	22.0	22.1	8.5	20.9	17.6	16.5
White race, %	96.8	97.1	100	98.5	90.0	94.2
Maternal AD, %	11.4	16.2	7.5	10.5	4.4	6.5
Maternal alcohol abuse, %	11.1	7.6	7.5	4.7	6.7	5.2
Maternal depression, %	17.2	19.1	17.0	14.9	14.3	23.9
Paternal psychiatric disorder, %†	23.5	13.2	13.8	16.4	15.4	5.1

Abbreviations: AD, alcohol dependence; DZ, dizygotic; MZ, monozygotic.
*Eighty-seven children of control twins had a previous diagnosis of alcohol abuse only. These cases were removed from the sample to add greater clarity to comparisons involving unaffected children.
†Based on previous *DSM-III-R* diagnoses of conduct disorder, antisocial personality disorder, and major depressive disorder; significant at *P*<.05; no other between-group comparisons were significant at *P*<.10.

Table 2. Crude Prevalence Rates for Alcohol Abuse (AA) and Alcohol Dependence (AD) by Age Group and Family Risk Status

Group	Participants, No.	Genetic/ Environmental Risk	Patients Aged 12-17 y, % (n = 416)		Patients Aged 18-26 y, % (n = 761)	
			AA Only	AD	AA Only	AD
MZ and DZ AD	587	High/high	9.9	3.5	24.4	18.5
MZ with abuse, co-twin AD	68	High/moderate	4.6	0	28.3	26.0
MZ unaffected, co-twin AD	94	High/low	2.9	0	15	11.7
DZ with abuse, co-twin AD	67	Moderate/moderate	11.5	0	26.8	9.8
DZ unaffected, co-twin AD	91	Moderate/low	2.7	2.7	16.7	11.1
MZ and DZ unaffected control twins	276	Low/low	7.5	2.1	19.2	10.4
Total	**1183**					

Abbreviations: DZ, dizygotic; MZ, monozygotic.

GROUP DIFFERENCES IN OFFSPRING OUTCOME

Table 2 gives prevalence rates for AA and AD across groups. As seen in **Table 3**, offspring of MZ and DZ twins with a history of AD (group 1: COAs) were significantly more likely to exhibit AA compared with offspring of nonalcoholic control fathers (group 6) after adjusting for covariates. In addition, offspring of AA MZ twins whose identical twin brothers were AD (group 2) were also more likely to exhibit AD than were offspring of nonalcoholic fathers (group 6). In contrast, none of the remaining risk groups (including group 3: offspring of a non-AA and non-AD MZ twin whose twin brother was AD) exhibited a significantly greater likelihood of AD or AA than did offspring of nonalcoholic control fathers.

Several covariates were related to offspring outcome after controlling for family risk status: offspring of divorced vs nondivorced fathers were more likely to exhibit AD; offspring older vs younger than 18 years of age (especially males) were more likely to exhibit AD or AA; and offspring born to fathers with more vs less than a high school education were more likely to develop AA. Paternal psychiatric comorbidity and maternal psychiatric status (including AD and AA) were not significantly related to outcome. That maternal AD or AA was unrelated of offspring outcome was probably the result of (1) the small number of mothers with either AA (8% of sample) or AD (10% of sample), which contributed to wide confidence intervals, and (2) the considerable number of unaffected mothers married to an AA or AD spouse (given our sampling design), which reduced differences between offspring with an affected vs an unaffected mother.

PLANNED COMPARISONS

Wald χ^2 tests for planned comparisons of offspring groups (all with 1 *df*) yielded several key findings. First, offspring at high genetic risk and high environmental risk (group 1) were no more likely to exhibit AA (χ^2=0.17; *P*=.68) or AD (χ^2=0.17; *P*=.68) than were offspring at high genetic and moderate environmental risk (group 2).

Table 3. Adjusted Relative Risk Ratios (95% Confidence Intervals) for *DSM-IV* Alcohol Abuse (AA) or Alcohol Dependence (AD) in Offspring as a Function of Family Risk Status and Pertinent Covariates From Multinomial Models

| | Offspring Outcomes | |
Variable	AA	AD
Group 6: MZ and DZ control	1.00	1.00
Group 1: MZ and DZ AD	1.63 (1.07-2.49)*	2.32 (1.40-3.86)*
Group 2: MZ abuser with AD co-twin	2.05 (0.88-4.74)	3.07 (1.29-7.27)†
Group 3: MZ unaffected with AD co-twin	0.74 (0.36-1.54)	0.80 (0.34-1.90)
Group 4: DZ abuser with AD co-twin	1.62 (0.76-3.48)	1.05 (0.39-2.82)
Group 5: DZ unaffected with AD co-twin	0.69 (0.30-1.58)	0.87 (0.34-2.27)
Maternal AD	1.42 (0.66-3.02)	0.72 (0.25-2.09)
Maternal AA	1.16 (0.60-2.23)	1.26 (0.62-2.57)
Maternal depression	1.09 (0.39-3.00)	2.54 (0.67-9.55)
Any paternal illicit drug abuse or dependence	0.81 (0.48-1.38)	0.69 (0.34-1.40)
Any paternal psychiatric disorder‡	0.87 (0.54-1.40)	0.94 (0.56-1.58)
Offspring age >18 y	3.08 (1.69-5.63)*	3.46 (1.55-7.75)*
Male offspring	0.79 (0.36-1.71)	0.47 (0.15-1.48)
Male offspring age >18 y	2.74 (1.16-6.44)†	5.36 (1.54-18.63)*
Greater than high school education	1.32 (1.10-1.58)*	1.18 (0.97-1.45)
Employed	1.86 (0.77-4.49)	0.74 (0.39-1.39)
Divorced	1.53 (1.00-2.34)*	1.76 (1.10-2.82)*

Abbreviations: DZ, dizygotic; MZ, monozygotic.
*$P<.05$.
†$P<.01$.
‡Major depression, antisocial personality disorder, or conduct disorder.

Compared with groups 1 and 2, offspring at high genetic but low environmental risk (group 3) were significantly less likely to exhibit AA ($\chi^2=6.02$; $P=.01$) or AD ($\chi^2=5.1$; $P=.24$), and this latter group did not differ in risk from those at moderate genetic but only low environmental risk (group 5) (AA: $\chi^2=0.02$; $P=.90$; AD: $\chi^2=0.03$; $P=.87$). Finally, risk differences between groups 1 and 2 and group 4 (moderate genetic risk and moderate environmental risk) approached significance for AD ($\chi^2=3.0$; $P=.08$) but not for AA ($\chi^2=0.00$; $P=.97$).

ASSESSING FOR GROUP DIFFERENCES IN GENETIC LIABILITY

To ensure that differences between groups 1 and 2 and group 3 resulted from the protective effects of a nonalcoholic family environment and not from differences in genetic liability, we examined offspring outcomes among 6 subgroups within group 1. Here, all twins, MZ or DZ, were AD, whereas co-twins could be (1) AD MZ, (2) AA MZ, (3) unaffected MZ, (4) AD DZ, (5) AA DZ, or (6) unaffected DZ. Using a multinomial logit model, results indicated that offspring of AD fathers whose MZ or DZ co-twins had a history of AA or AD were no more likely to exhibit AA or AD compared with offspring of AD fathers whose MZ or DZ co-twins were not affected. Odds ratios ranged from 1.00 to 1.83, and all are associated with 95% confidence intervals that included unity. Furthermore, results confirmed the homogeneity of odds ratios for group 1 across co-twin zygosity. Odds ratios ranged from 0.43 to 1.46, and all were associated with 95% confidence intervals that included unity. These results suggest that an offspring with an alcoholic father whose cotwin is not affected is at no less genetic risk than the child of an AD father whose co-twin is AA or AD.

COMMENT

Although the familial transmission of alcoholism risk is beyond doubt, there has been continuing controversy as to the nature of these familial effects for many decades. Many psychosocial researchers and most clinicians, for example, argue that parental alcoholism alters the family environment and that these family changes—be they disturbances in parenting, the parent-child relationship, modeling effects, economic stability, or more general family-level disturbances—are the operative effects for explaining the eventual development of alcoholism. For these observers, the conclusion that genetic and environmental effects matter but that the latter are not systematically related to what happens within the family to make siblings alike would be vigorously disputed. Given the serious and recent criticisms of the behavioral genetic perspective,[18,23,42,43] together with concerns that geneticists themselves have discussed regarding limitations to their approach,[6,23] continued examination of the etiology of alcoholism remains essential.

The offspring-of-twins design offered a relatively strong test of the hypothesis that family environmental effects make a difference in accounting for offspring outcomes. Four of our findings are particularly noteworthy.

First, offspring of alcoholic fathers (group 1) were at significantly higher risk for alcohol-use disorders than were offspring of controls (group 6: low genetic and low environmental risk), results that concur with the often reported finding that alcoholism "runs in families."[44] Although such a finding is "necessary" for building a family theory of alcoholism, it tells us little about the nature of the family effects, hence the need for more informative group contrasts that help specify the nature of such family relatedness.

Second, the contrast between groups 1 and 3 speaks most clearly to the impact of nongenetic family effects on offspring alcoholism. That is, in the absence of an alcoholic family environment—even with high genetic risk for the disorder—offspring alcoholism outcomes were similar to those of controls (low genetic and low environmental risk). Furthermore, there seemed to be no difference in impact on offspring of paternal AD (group 1) and paternal AA (group 2) as long as the father had an AD MZ co-twin. Offspring in both of these groups were similarly at heightened risk for alcohol-use disorders, and both were at greater risk than offspring from group 3. Stated otherwise, given a background of heightened genetic risk, moderate levels of paternal alcohol-related problems (paternal abuse) provided no protection compared with severe levels of paternal alcohol-related problems (paternal dependence). What this means—if the present findings prove to be replicable and generalizable—is that genetic risk in many cases becomes actualized only if there is some significant environmental sequela to the genetic vulnerability. That is, genetic risk may be necessary but not sufficient for offspring alcoholism to develop. Although we cannot yet specify what particular family environmental factors are present when the father expresses AA or AD and absent when he does not, the larger alcoholism literature has suggested various possibilities: the impact of paternal AD on marital and parent-child relationships; drinking models and drinking-relevant cognitions and experiences; increased risks of traumatic experiences such as rape, molestation, and physical abuse[45]; and the family's economic well-being.[2,7,24]

What we do know, however, is that the outcome differences between groups 1 and 3 cannot be accounted for by group differences in maternal AD, depression, or antisociality or in paternal depression, antisociality, or educational and occupational status; that is, these variables were covariates in our primary analyses. Neither can these differences be explained by differences in genetic liability for groups 1 and 3 given our findings that offspring of AD fathers whose MZ or DZ co-twin had a history of either AD or AA were no more likely to exhibit AA or AD than were offspring of AD fathers with an unaffected MZ or DZ co-twin. Further clarification of specific family environmental effects that differentiate the environments of families with and without an AD father would be of great importance.

It is straightforward to reconcile these findings with results from twin studies of AD and AA. In the traditional twin design, comparing MZ and DZ twin pairs reared together, genetic effects and gene × shared environment interaction effects are confounded.[46] The relatively weak evidence for shared environment effects on AD risk from such twin studies[47-50] would be consistent with the notion that the environmental effects associated with parental AD or AA are dependent on offspring genotype, that is, that genotype × shared environmental interaction effects are important.[41] On the other hand, adoption studies have not, in general, suggested an important role for alcoholism in adoptive parents in the transmission of alcoholism risk.[9] In attempting to reconcile our results with this literature, several possible explana-

tions can be offered. Typically, as in the case of the Iowa adoption studies[51] and the Swedish adoption studies,[52,53] alcoholism cases were identified from official records and thus may have disproportionately represented the most severe alcoholic individuals and those with antisocial traits, for example, the elevated rates of temperance board registrations of biological fathers compared with general population rates in the Stockholm Adoption Study.[54] Given these considerations, it seems plausible the these offspring are at very high levels of genetic risk. In general population samples, however, such as those represented in the Virginia, Australian, and Vietnam Era twin samples, only a few AD cases will be severely affected. The high prevalence of *DSM-III-R* AD in the Vietnam Era Twin Registry sample, which reflects the rather broad definition of the disorder in this registry, is consistent with the contention that we are dealing with, on average, less severe cases of paternal AD and thus lower levels of genetic risk in the offspring.[50] In light of these considerations, we suggest that for individuals with the highest levels of genetic risk, shared environmental and genotype × shared environment effects on risk may be relatively unimportant but that for individuals with less extreme levels of genetic risk (who may well represent most individuals who become AD in the general population), genetic and genotype × shared environment interaction effects may assume greater importance in determining offspring outcomes.

A third finding was related to our expectation that children of unaffected fathers would fare better than children of AA fathers and that both would fare better than children of AD fathers. But as seen, the offspring of AA fathers looked very much like their counterparts with AD fathers, meaning that there was no "partial" protection associated with the milder forms of the disorder within the MZ group. The absence of such a continuum of effect may be understood in several ways: (1) high-risk environmental exposure associated with paternal AA is sufficiently disruptive to potentiate the genetic risk into expressed disorder; (2) there may have been various episodes of abuse during the father's parenting years that translated into a more chronic course and therefore a significant impact on the family environment (both of these explanations seem to be consistent with our finding in the Vietnam Era Twin Registry twins that AA and AD share genetic and family environmental risk factors in common); and (3) some of the AA diagnoses may have arisen because of underreporting of symptoms when in fact AD would have been the more appropriate diagnosis.

A final result was the absence of differences between groups 3 and 5 (ie, between offspring of unaffected twins with AD MZ co-twins vs AD DZ co-twins) and the absence of differences between the controls (group 6) and all moderate-risk groups (ie, offspring from groups 3, 4, and 5). As recalled, our hypotheses were based on theoretical considerations regarding different levels of genetic and environmental risk associated with group status. For example, group 3 is at higher genetic risk than groups 4, 5, or 6, whereas groups 4 and 5 are at the same genetic risk, but group 4 is at higher environmental risk than group 5, whereas group 5 is at higher genetic risk (but similar environmental risk) than group 6, and so on.

In considering the findings that differences in the prevalence of offspring AA and AD were not ordered in terms of these expectations (ie, group 3>group 4>group 5>group 6), it should be remembered that the prevalence of alcohol-use disorders is at its highest during the adolescent to young adult years[55,56] so that it may be more difficult to differentiate offspring risk at this age in terms of our varying genetic and environmental profile. Our sample contained many minors who have not yet passed through the major risk period for the development of alcohol-use disorders.[55] With the passage of time, however, those at lower risk would be expected to adopt patterns of nonproblem drinking, whereas those at higher risk would be expected to exhibit continuous or intermittent problems of AA or AD.[57,58] If true, future follow-up assessments of this sample should provide additional information on this issue, which, in turn, would motivate us to revisit our study hypotheses.

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REFERENCES

1. McGue M. A behavioral-genetic perspective on children of alcoholics. *Alcohol Health Res World.* 1997;21:210-217.
2. Sher KJ. Psychological characteristics of children of alcoholics. *Alcohol Health Res World.* 1997;21:247-254.
3. Sher KJ. *Children of Alcoholics: A Critical Appraisal of Theory and Research.* Chicago, Ill: University of Chicago Press; 1991.
4. Windle M. Concepts and issues in COA research. *Alcohol Health Res World.* 1997; 21:185-191.
5. Windle M, Searles J. *Children of Alcoholics: Critical Perspectives.* New York, NY: Guilford Publications; 1990.
6. Jacob TJ, Sher K, Bucholz KK, True WT, Sirevaag EJ, Rohrbaugh J, Nelson E, Neuman RJ, Todd RD, Slutske WS, Whitfield JB, Kirk K, Martin NG, Madden PAF, Heath AC. An integrative approach for studying the etiology of alcoholism and other addictions. *Twin Res.* 2001;4:103-118.
7. Jacob T, Leonard K. Family and peer influences in the development of adolescent alcohol abuse. In: Zucker R, Boyd G, Howard J, eds. *Development of Alcohol Problems: Exploring the Biopsychosocial Matrix of Risk.* Washington, DC: National Institute on Alcohol Abuse and Alcoholism; 1994.
8. Ellis DA, Zucker RA, Fitzgerald HE. The role of family influences in development and risk. *Alcohol Health Res World.* 1997;21:218-226.
9. Heath AC, Slutske WS, Madden PAF. Gender differences in the genetic contribution to alcoholism risk and to alcohol consumption patterns. In: Wilsnack RW, Wilsnack SC, eds. *Gender and Alcohol.* Rutgers, NJ: Rutgers University Press; 1997.
10. Johnson S, Jacob T. Psychosocial functioning in children of alcoholic fathers. *Psychol Addict Behav.* 1995;9:101-113.
11. Chassin L, Barrera M. Substance use escalation and substance use restraint among adolescent children of alcoholics. *Psychol Addict Behav.* 1993;7:3-20.
12. Jacob T, Windle M. Young adult children of alcoholic, depressed and nondistressed parents. *J Stud Alcohol.* 2000;61:836-844.
13. Newcomb MD, Felix-Ortiz M. Multiple protective and risk factors for drug use and abuse: cross-sectional and prospective findings. *J Pers Soc Psychol.* 1992; 63:280-296.
14. Sher KJ, Trull TJ. Methodological issues in psychopathology research. *Annu Rev Psychol.* 1996;47:371-400.
15. Zucker RA, Fitzgerald HE, Moses HD. Emergence of alcohol problems and the several alcoholisms: a developmental perspective on etiologic theory and life course trajectory. In: Cicchetti D, Cohen DJ, eds. *Developmental Psychopathology: Risk, Disorder, and Adaptation.* Vol 2. New York, NY: John Wiley & Sons Inc; 1995: 677-711.
16. Heath AC. Genetic influences on alcoholism risk? a review of adoption and twin studies. *Alcohol Health Res World.* 1995;19:166-171.
17. Eaves LJ, Silberg JL, Meyer JM, Maes HH, Simonoff E, Pickles A, Rutter M, Reynolds CA, Heath AC, Truett KR, Neale MC, Erikson MT, Loeber R, Hewitt JK. Genetics and developmental psychopathology, 2: the main effects of genes and environment on behavioral problems in the Virginia Twin Study of Adolescent Behavior Development. *J Child Psychol Psychiatry.* 1997;38:965-980.
18. Stoolmiller M. Implications of restricted range of family environments for estimates of heritability and nonshared environment in behavior-genetic adoption studies. *Psychol Bull.* 1999;125:392-409.
19. Bouchard TJ, Pederson N. Twins reared apart: nature's double experiment. In: LaBuda MC, Grigorenko EL, eds. *On the Way to Individuality: Current Methodological Issues in Behavioral Genetics.* Hungtington, NY: Nova Science Publishers; 1999:71-93.
20. Gottesman II, Bertelsen A. Confirming unexpressed genotypes for schizophrenia. *Arch Gen Psychiatry.* 1989;46:867-872.
21. Heath AC, Kendler KS, Eaves LJ, Markell D. The resolution of cultural and biological inheritance: informativeness of different relationships. *Behav Genet.* 1985; 15:439-465.
22. Nance WE, Corey LA. Genetic models for the analysis of data from the families of identical twins. *Genetics.* 1976;83:811-826.
23. Rutter M, Pickles A, Murray R, Eaves L. Testing hypotheses on specific environmental causal effects on behavior. *Psychol Bull.* 2001;127:291-324.
24. Jacob T. Family studies of alcoholism. *J Fam Psychol.* 1992;5:319-338.
25. Steinglass P, Bennett LA, Wolin SJ, Reiss D. *The Alcoholic Family.* New York, NY: Basic Books Inc Publishers; 1987.
26. VanOers JA, Bongers IM, VanDeGoor LA, Gerresten HF. Alcohol consumption, alcohol-related problems, problem drinking, and socioeconomic status. *Alcohol Alcohol.* 1999;34:78-88.
27. Bucholz KK, Heath AC, Madden PAF. Transitions in drinking in adolescent females: evidence from the Missouri adolescent female twin study. *Alcohol Clin Exp Res.* 2000;24:914-923.
28. Bucholz KK, Heath AC, Reich T, Hesselbrock VM, Kramer JR, Nurnberger JI, Schuckit MA. Can we subtype alcoholics? a latent class analysis of data from relatives of alcoholics in a multicenter family study of alcoholism. *Alcohol Clin Exp Res.* 1996;20:1462-1471.
29. Jackson KM, Sher KJ, Wood PK. Trajectories of concurrent substance use disorders: a developmental, typological approach to comorbidity. *Alcohol Clin Exp Res.* 2000;24:902-913.
30. Eisen S, True W, Goldberg J, Henderson W, Robinette CD. The Vietnam Era Twin (VET) Registry: method of construction. *Acta Genet Med Gemellol (Roma).* 1987; 36:61-67.
31. Henderson WG, Eisen S, Goldberg J, True W, Barnes JE, Vitek ME. The Vietnam Era Twin Registry: a resource for medical research. *Public Health Rep.* 1990; 105:368-373.
32. Eisen SA, Goldberg J, True WR, Henderson WR. A co-twin control study of the effects of the Vietnam War on the current physical health of veterans. *Am J Epidemiol.* 1991;134:49-58.
33. Tsuang MT, Lyons MJ, Eisen S, Goldberg J, True W, Meyer J, Eaves L. Genetic influences on *DSM-III-R* drug abuse and dependence drugs: a study of 3,372 twin pairs. *Am J Med Genet.* 1996;67:473-477.
34. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition.* Washington, DC: American Psychiatric Association; 1987.
35. Bucholz KK, Cadoret R, Cloninger CR, Dinwiddie SH, Hesselbrock VM, Nurnberger JI, Reich T, Schmidt I, Schuckit MA. A new, semi-structured psychiatric interview for use in genetic linkage studies: a report of the reliability of the SSAGA. *J Stud Alcohol.* 1994;55:149-158.
36. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.* Washington, DC: American Psychiatric Association; 1994.
37. Skinner HH, Sheu WJ. Reliability of alcohol use indices: Lifetime Drinking History and MAST. *J Stud Alcohol.* 1982;43:1157-1170.
38. Stata Corp. *Stata Statistical Software.* College Station, Tex: Stata Corp; 2001.
39. Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. The lifetime history of major depression in women: reliability of diagnosis and heritability. *Arch Gen Psychiatry.* 1993;50:863-870.
40. Neale MC, Maes HH. *Methodology for Genetic Studies of Twins and Families.* Dordrecht, the Netherlands: Kluwer Academic Publishers; 2000.
41. Heath AC, Nelson EC. Towards a molecular epidemiology of alcohol depen-

dence: the importance of genotype × environment interaction effects. *Alcohol Res Health.* 2002;26:193-201.

42. Searles JS. The role of genetics in the pathogenesis of alcoholism. *J Abnorm Psychol.* 1988;97:153-167.

43. Stoolmiller M. Correcting estimates of shared envrionental variance for range restriction in adoption studies using a truncated multivariate normal model. *Behav Genet.* 1998;28:429-441.

44. Cotton NS. The familial incidence of alcoholism: a review. *J Stud Alcohol.* 1979; 40:89-116.

45. Elliot CN, Heath AC, Madden PAF, Cooper ML, Dinwiddie SH, Bucholz KK, Glowinski A, McLaughlin T, Dunne MP, Statham DJ, Martin NG. Association between self-reported childhood sexual abuse and adverse psychosocial outcomes. *Arch Gen Psychiatry.* 2002;59:139-145.

46. Eaves LJ, Last KA, Martin NG, Jinks JL. A Progressive approach to non-additivity and genotype-environmental covariance in the analysis of human differences. *Br J Math Stat Psychol.* 1977;30:1-42.

47. Kendler KS, Heath AC, Neale MC, Kessler RC, Eaves LJ. A population-based twin study of alcoholism in women. *JAMA.* 1992;268:1877-1882.

48. Prescott CA, Aggen SH, Kendler KS. Sex differences in the sources of genetic liability to alcohol abuse and dependence in a population-based sample of US twins. *Alcohol Clin Exp Res.* 1999;23:1136-1144.

49. Heath AC, Bucholz KK, Madden PAF, Dinwiddie SH, Slutske WS, Statham DJ, Dunne MP, Whitfield J, Martin NG. Genetic and environmental contributions to alcohol dependence risk in a national twin sample: consistency of findings in women and men. *Psychol Med.* 1997;27:1381-1396.

50. True WR, Xian H, Scherrer JF, Madden PAF, Bucholz KK, Heath AC, Eisen SA, Lyons MJ, Goldberg J, Tsuang M. Common genetic vulnerability for nicotine and alcohol dependence in men. *Arch Gen Psychiatry.* 1999;56:655-661.

51. Cadoret R, Troughton E, Woodworth G. Evidence of heterogeneity of genetic effect in Iowa adoption studies. *Ann N Y Acad Sci.* 1994;708:59-71.

52. Cloninger CR, Bohman M, Sigvardsson S. Inheritance of alcohol abuse: cross-fostering analysis of adopted men. *Arch Gen Psychiatry.* 1981;38:861-868.

53. Sigvardsson S, Bohman M, Cloninger CR. Replication of the Stockholm Adoption Study of alcoholism: confirmatory cross-fostering analysis. *Arch Gen Psychiatry.* 1996;53:681-687.

54. Cloninger CR, Bohman M, Sigvardsson S, Von Knorring AL. Psychopathology in adopted-out children of alcoholics: the Stockholm Adoption Study. *Recent Dev Alcohol.* 1985;3:37-51.

55. Johnston LD, O'Malley PM, Bachman JG. *National Survey Results on Drug Use From the Monitoring the Future Study, 1975-1997: Volume II: College Students and Young Adults.* Rockville, Md: National Institute on Drug Abuse; 1998.

56. Muthen BO, Muthen LK. The development of heavy drinking and alcohol related problems from ages 18 to 37 in a US national sample. *J Stud Alcohol.* 2000;61: 290-300.

57. Schulenburg J, Wadsworth KM, O'Malley PM, Bachman JG, Johnston LD. Adolescent risk factors for binge drinking during the transition to young adulthood: variable- and pattern-centered approaches to change. *Dev Psychol.* 1996;32: 659-674.

58. Jackson KM, Sher KJ, Gotham HJ, Wood PK. Transitioning into and out of large-effect drinking in young adulthood. *J Abnorm Psychol.* 2001;110:378-391.