# Searching for the Full Picture: Structural Equation Modeling in Alcohol Research

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This article summarizes the proceedings of a symposium presented at the 2005 Research Society on Alcoholism meeting in Santa Barbara, California. This symposium begins with a description by Michael Windle of structural equation modeling (SEM), including the assets and liabilities of this approach. Next, Marc Schuckit and Tom Smith demonstrate the application of an SEM approach to understanding the impact of a low level of response to alcohol, using data from both adolescent and adult populations. Victor Hesselbrock and colleagues next review the results when an SEM approach is used in the longitudinal study of externalizing behaviors. This is followed by a description of the application of SEM to an affect-related model as discussed by John Kramer and Kathleen Bucholz. Finally, Kenneth Sher offers thoughts on how to place these findings into perspective.

**Key Words:** Alcohol, Genetics, Structural Equation Models.

OUR UNDERSTANDING OF factors that contribute to alcohol use, problems, and alcohol use disorders (AUDs) is expanding rapidly. On the one hand, researchers are identifying genetically influenced intermediate characteristics that explain about half of the variance for the AUD risk. These efforts have led to the search for genes that affect these intermediate phenotypes (also known as endophenotypes) in mediating and moderating the predisposition for heavier drinking and associated problems. At the same time, both cross-sectional and longitudinal studies are revealing an expanding number of sociocultural and additional environmental characteristics that also affect drinking behaviors and problems.

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One subsequent challenge is to test the genetically influenced endophenotypes and additional "environmental" characteristics in an integrated model of risk. This is especially relevant to questions relating to how intermediate phenotypes of alcohol-metabolizing enzymes, level of response to alcohol, acting out or externalizing behaviors, and mood and anxiety symptoms (i.e., internalizing behaviors) relate to additional life variables while impacting on drinking behaviors (Schuckit, 2002). The relatively recent development of structural equation modeling (SEM) has opened new doors in our search for ways to evaluate the interrelationships among these complex phenomena (Jöreskog, 1993).

This symposium begins with a description by Michael Windle of SEM, including the assets and liabilities of this approach. Next, Marc Schuckit and Tom Smith demonstrate the application of an SEM approach to understanding the impact of a low level of response (LR) to alcohol, using data from both adolescent and adult populations. Victor Hesselbrock and colleagues next review the results when an SEM approach is used in the longitudinal study of externalizing behaviors. This is followed by a description of the application of SEM to an affect-related model as discussed by John Kramer and Kathy Bucholz. Finally, Ken Sher offers thoughts on how to place these findings into perspective.

## PROMISES AND PITFALLS OF SEM

*Michael Windle*

Over the past 20 to 25 years, SEM has flourished with respect to an expanding range of statistical models and research applications across substantive domains ranging from neuroimaging to marketing research to the evalua-

tion of multilevel models of neighborhood effects on phenotypes of interest. This contribution focuses on 4 topics, (1) a brief history of SEM; (2) major strengths and promises of this approach; (3) a "sampling" of SEM applications; and (4) major limitations and pitfalls of such modeling.

*Brief History of SEMs.* There was a confluence of factors in the 1970s and the early 1980s that contributed to the evolution of SEMs as we know them today. A necessary condition was the proliferation of computer technology that enabled the development and application of rapid computational and numerical algorithms to facilitate an expanded range of statistical models with different distributional assumptions and alternative estimation procedures. Factor analytic applications that used to take weeks to months to compute were reduced to a few seconds (or less) on current computers.

There was also a convergence of statistical modeling procedures from 3 different sources. First, econometricians had been intensively involved in the development of multiequation statistical models for continuous and categorical variables and for limited dependent variables (e.g., truncated and censored distributions). Second, sociologists had turned their attention to the development of path analytic models to specify and test theoretical models of interrelationships among manifest (measured) variables. Third, psychologists and educational psychologists had focused on the development of measurement, or latent variable, models. Structural equation modeling combined these 3 influential streams of thought and activity to provide a methodological approach that used multiequation systems with latent variables that could be specified to test theoretical models.

*Major Strengths and Promises of SEM.* As a methodological approach, there are 3 major advantages to SEM relative to more traditional ANOVA and regression approaches. First, SEM has much stronger theory testing capability in specifying, estimating, and evaluating complex multivariate statistical models that correspond to hypothesized network(s) of interrelationships among variables. Theoretically based notions and specific models can assume a range of forms from the specification of how items or variables should "load" on specified factors; to elaborations of multiple mediator and moderator models; to comparative models of prediction across sex, racial/ethnic, or cross-cultural groups; and to complex longitudinal models that involve alternative models of change and alternative structures for correlated residuals. Importantly, a goal of SEM is to reproduce the observed variance–covariance matrix via a specified (or hypothesized) model. To evaluate the adequacy to which a hypothesized model achieves this objective, a number of goodness of model fit statistics are provided in SEM output. Hence, SEM provides a hypothesis-driven framework in which specified models can be rejected; i.e., the hypothesized model may not adequately reproduce the observed variance–covariance matrix and the goodness of model fit statistics provide an analytical method of evaluating the specified model hypothesis. If the specified model does not fit, detailed output (e.g., modification indexes) provides information as to which parameters need to be freely estimated to improve model fit. One can also specify a sequence of nested models to test alternative models that may be specified to account for the observed data.

The second advantage is that SEMs are extremely flexible in specifying, estimating, and evaluating a broad range of continuous and categorical models within a common framework. Consequently, separate programs do not have to be used to conduct logistic regression, ordered regression, and standard linear regression models. Likewise, SEM can easily accommodate the specification of multiple latent variables within a single model and simultaneously estimate specified predictive relations among the latent variables or among the latent variables and a set of manifest variables. Many SEM programs also have a range of alternative estimators to accommodate nonnormally distributed data, as well as methods to address missing value data estimation. The unifying approach of SEM across a broad range of statistical models may be a great aid to new generations of investigators and overcome some of the limitations of educational training of previous generations who were often taught to think in single-model terms (e.g., experimental psychologists were commonly taught ANOVA models and individual difference psychologists were taught correlation/regression models).

A third advantage of SEM is that there has been a rapid expansion of more user-friendly software programs, workshops, and online resources (e.g., Q&A sessions on SEM Web pages) that have fostered ease of use and exchange of information. A number of authors now make the command syntax, data set, and output of some of their SEM applications available online. This more open exchange of information and sharing of resources are likely to continue the widespread impact of SEM.

*A "Sampling" of SEM Applications.* Our group has used SEMs in a range of applications with the Lives Across Time: A Longitudinal Study of Adolescent and Adult Development (LAT). The LAT is currently in its 17th year of funding and is an ongoing prospective study of adolescents and their parents. The purpose of LAT is to investigate developmental processes and the roles of risk and protective factors that contribute to alcohol use, alcohol disorders, and other health outcomes from adolescence through adulthood (for a more complete description of the LAT, see Windle and Wiesner, 2004). A number of these SEM applications to LAT data are provided in the reference section, but I will briefly describe a few to provide a flavor of the kinds of SEM applications that are possible. In one application (Windle and Mason, 2004), we used SEM to evaluate the multiproblem factor structure of 14 variables, yielding the 4 latent variables of Polydrug Use, Delinquency, Negative Affect, and Academic Orientation. We then

used 11 risk and protective factors to predict these 4 latent variables to determine which ones were more general (e.g., significantly predicted 3–4 of the latent variables) or specific (e.g., significantly predicted only one of the latent variables). The findings of such a model could be important in informing intervention programs regarding which factors to target for which problems. A second application (Windle et al., 2005) used latent growth mixture modeling to study subgroup patterns of change in heavy episodic drinking (HED) across the age range of 16 to 25 years. For males, 4 different patterns emerged, including one characterized as a Non-HED Stable Group, a second as a Moderate HED Group (averaged about 1 heavy drinking episode per month across time), the third as a High HED Stable Group (averaged between 2 and 4 heavy drinking episodes per month across time), and the fourth as a Chronic HDE Group (averaged 9 or more heavy drinking episodes per month across a large portion of time). Predictors were used to distinguish the 4 groups to determine which factors may be most influential in impacting the respective trajectories; such information may be used to target significant factors that may be more relevant for 1 group (e.g., the Chronic HDE Group) than for others. Although we have often used these SEM applications with repeated-measures correlational data, it is important to note that SEM can be usefully applied to experimental research designs, including intervention research applications.

*Major Limitations and Pitfalls of SEM.* Unfortunately, SEMs also have a number of limitations and potential pitfalls. First, for applications with multivariate correlational data, SEMs do not provide a solid basis for inferring causality. Rather, SEMs can provide plausible representations of data structures and can specify and test statistical models in which such representations can be statistically rejected. The strength, or plausibility, of a specified model may be supported not only by goodness-of-fit indexes but also by other criteria such as ruling out alternative (e.g., third variable) "causes" and via model comparisons with alternative structural representations of the data. Second, it is often possible to reproduce the observed variance–covariance data with more than one model specification, thereby producing statistically equivalent models. Under these circumstances, nonstatistical considerations and other sources of support are required to distinguish among models. Third, in practice there are often excessive model modifications (e.g., freeing additional parameters based on previous models) with the same sample, and such information is not shared with the readership. The reason why this is important is because the findings from such applications may not replicate (because of capitalization on sample-specific fluctuations) and there is a major blurring of the distinction between more confirmatory, hypothesis-driven modeling and more descriptive, exploratory modeling. Fourth, there remain technical issues surrounding the modeling of latent variable interactions and the modeling of nonlinear relationships and alternative distributional forms. These issues are important in addressing key features of many theories and models (e.g., diathesis-stress model) and accommodating data that are not best represented via a linear model.

*Conclusions.* In summary, SEM is a useful tool for purposes of conceptualization, measurement, and analyses of networks of interrelationships among variables. However, it is not a substitute for the selection of poor measures or of an inadequate research design.

## EVALUATION OF THE LEVEL OF RESPONSE TO ALCOHOL—SOCIAL INFORMATION PROCESSING MODEL IN 2 POPULATIONS

*Marc A. Schuckit and Tom L. Smith*

*Introduction.* Alcohol use disorders are complex genetically influenced conditions where genes explain up to 60% of the risk (Prescott and Kendler, 1999; Schuckit, 2002). Multiple genetically influenced phenotypes contribute to the vulnerability, including a low level of response to alcohol (Schuckit, 2002). With an estimated heritability between 40 and 60%, a low LR predicts heavier drinking and alcohol-related outcome and appears to operate independent of additional intermediate phenotypes such as externalizing behaviors and peripheral alcohol-metabolizing enzymes (Li, 2000; Schuckit et al., 2000, 2004a).

Because environmental influences also explain a large proportion of the risk for heavier drinking and alcohol-related problems, the impact of any specific gene or of the broader LR intermediate phenotype can only be optimally understood when evaluated in the context of additional environmental contributors (Moffitt et al., 2005). Therefore, this presentation reviews information from 2 recent publications evaluating the ability of a low LR to alcohol to predict future heavier drinking and alcohol-related problems in the context of additional important life domains (Schuckit et al., 2004b, 2005).

*Methods.* In the first study, approximately 300 Caucasian males from the San Diego Prospective Study had been evaluated with an alcohol challenge to determine their intensity of reaction to alcohol at a given blood alcohol level at about age 20, with more than 95% successfully followed 15 and 20 years later (Schuckit et al., 2004b). As described in a recent paper, data were available on the family history of AUDs (FHalc) as established from the original evaluation and both follow-ups; the level of response to alcohol using alcohol challenges at age 20; expectations of the effects of alcohol as measured at the 15-year follow-up (EXPECT15) using all 6 scales of the Alcohol Expectancy Questionnaire (AEQ-A); drinking among important peers at 2 recent follow-up points (PEER15 and PEER25) using the Important People and Activities Scale; the use of alcohol to cope with life stress (COPE15 and COPE20) was taken from the Drinking to Cope Scale; and alcohol-related outcomes (ALCOUT) focused on the number of

Diagnostic and Statistical Manual of Mental disorders (DSM) dependence and abuse problems.

The second study evaluated data from 238 12- to 19-year-olds (mean age 17 years), about 50% of whom were male, from the Collaborative Study on the Genetics of Alcoholism (COGA) (Schuckit et al., 2005). For this investigation, FHalc was determined from data available through COGA interviews; the LR to alcohol used self-report retrospective scores of the number of drinks required for various effects early in the drinking career from the ''First 5 times drinking'' score taken from the Self-Rating of the Effects of Alcohol (SRE) measure; the HOME environment was evaluated on drinking practices of parent figures in the teenagers' homes; EXPECT used the adolescent version of the AEQ-A; and ALCOUT were defined for these teens using a combination of the maximum number of drinks consumed and the number of alcohol problems.

For each study, data were entered into an Analysis of Moment Structures (AMOS) Structural Equation Program using a variance/covariance matrix that invoked maximum likelihood estimation (Arbuckle and Wothke, 1999). Tests of mediation used both the Sobel Test and an evaluation of the model both with and without direct effects involved in potential mediational relationships, comparing the resulting chi-square.

*Results.* For the adults from the San Diego Prospective Study, the resulting LR-based model explained 58% of the 20-year outcome (Schuckit et al., 2004b). Here, FHalc related both to LR at age 20 and to alcoholic outcomes 20 years later. Level of response operated in part through how a person coped with stress, with the latter also contributing to alcoholic outcomes while serving as a partial mediator of the relationship between LR and ALCOUT. The impact of drinking among peers and expectations of the effects of alcohol in this model using adult subjects was primarily to enhance alcoholic outcomes both directly and through drinking to cope. This analysis confirmed the importance of LR in a model of alcoholic outcome where it appears to work primarily through drinking to cope rather than via drinking among peers or expectations of the effects of alcohol, although the relationship between LR and expectations was 0.08 and just narrowly missed being significant.

For the COGA-based model tested in teenagers, 49% of the variance was explained by the SEM (Schuckit et al., 2005). Here, once again, LR related to both FHalc and ALCOUT. In these teenagers, however, LR predicted alcohol expectancies, which, in turn, functioned as a mediator of the relationship between LR and alcoholic outcomes. Drinking in the home was, as expected, related to FHalc, and while not directly linked to LR, did significantly influence expectations of the effects of alcohol. The final model did not significantly differ by sex or with age.

*Conclusions.* These evaluations advance our understanding of how the genetically influenced intermediate phenotype of a low LR to alcohol impacts on heavier drinking and alcohol-related problems. While not all domains were available for each of the models, SEM evaluations in both adults and teenagers confirm the ability of an FH of AUDs to predict a low LR to alcohol, which, in both models, was related to alcoholic outcomes. In the adults, the low LR appeared to operate primarily through the use of alcohol to cope with stress. In the teenagers, while a measure of drinking to cope was not available in the COGA population, the low LR appeared to operate primarily through altering the expectations of the effects of alcohol.

Future research will seek to evaluate the exact same domains in 2 generations from the San Diego Prospective Study, including models using the original probands who entered the investigation almost 25 years ago, as well as their approximately 600 children who are currently in their early teens. The results of SEM models using characteristics such as LR will improve our ability to identify specific environmental risk factors that might be amenable to change that can be used in prevention efforts attempting to diminish the risk for heavier drinking and AUDs in individuals with a low LR to alcohol. Such studies, as well as evaluations of models using specific genes that contribute to LR rather than the broad low response phenotype, may also facilitate the search for subgroups of alcoholic individuals who might respond better to one versus another treatment approach and might lead the way toward the development of new treatments in the future (Hu et al., 2005; Wilhelmsen et al., 2003).

## DEVIANCE PRONENESS AND THE RISK FOR ALCOHOL DEPENDENCE

*Victor Hesselbrock, Christine Ohannessian, Susan Averna, and Lance Bauer*

The ''Deviance Proneness'' model of vulnerability (Sher, 1991) for predicting pathological alcohol involvement was tested using data from an ongoing study of an ethnically diverse community sample of adolescent and young adult males and females at risk for developing alcohol problems. The initial data were collected in 1992 to 1997 ($n = 338$) when subjects were in midadolescence (16–17 years of age), with a focus on the initiation and maintenance of drinking behaviors. The T2 follow-up focused on early adulthood (21–22 years of age) and covered the years when subjects were at maximal risk for heavy drinking and developing a variety of alcohol problems, including pathological alcohol involvement. The T3 follow-up data are currently being collected; subjects are 26 to 27 years old at this interval. These data were used to test the model for predicting alcohol use problems (''pathological alcohol use''). The stability and efficiency of the model for predicting pathological alcohol involvement across the 3 points in time were also examined.

A sample of 148 boys and 190 girls completed the baseline assessment battery, with approximately 85% completing the T2 assessment and, to date, 78% of the T3 follow-up. The average age of the sample at baseline was 16.5 years for both boys and girls, and subjects had completed 10.2 years of primary education (9.9 for boys; 10.2 for girls). To control for fetal alcohol effects, a lifetime history of DSM-III-R maternal alcohol or other substance dependence was an exclusionary criterion. However, 62% ($N = 211$) of the subjects had a biological father with a lifetime history of DSM-III-R alcohol dependence, and 28% of these fathers also had a history of antisocial personality disorder. A sample of 127 control subjects whose biological parents had no history of DSM-III-R alcohol or substance dependence or abuse was also recruited (Table 1). At baseline, none of the adolescents had a history of DSM-III-R alcohol or drug abuse or dependence, although many reported use of alcohol, tobacco, marijuana, and other drugs. All subjects completed an assessment battery that included a psychiatric history (C-SSAGA-II instruments from the COGA), a COGA-based family history assessment (FHAM, Rice et al., 1995), personality traits [e.g., the NEO Five Factor Inventory (Costa and McCrae, 1986)], Sensation Seeking Scale v5 (Zuckerman, 1984), the AEQ-A (Brown et al., 1980), the Positive and Negative Affect Scale or PANAS (Diener et al., 1985), and measures of social support from family and friends (Procidano and Heller, 1983).

Structural equation methods (AMOS, v4.0) were used to test the Deviance Proneness model for predicting the onset of alcohol, tobacco, and marijuana use, and onset of alcohol problems in cross-sectional analyses at each time point as well as across the 3 time points. A number of potential moderators and mediators of vulnerability for early alcohol use and problems outcomes due to a family history of alcohol dependence were examined. The predictor variables considered included personality/temperament, childhood conduct problems, negative affectivity, social support from friends and family, and alcohol expectancies.

At T1, a paternal family history of alcohol or drug dependence was not found to be directly associated with either initiation of use or onset of alcohol or drug problems. However, as predicted by the Deviance Proneness model, Conduct Problems (as measured by the number of lifetime childhood conduct problems reported) were predictive ($\beta = -0.21$) of the onset of alcohol, tobacco, and marijuana substance use. Behavioral Undercontrol, the latent trait defined by the temperament traits of disinhibition and boredom susceptibility, predicted Conduct Problems ($\beta = 0.54$).

At T1, early onset of alcohol use ($\beta = -0.21$), but not other substances, in turn predicted quantity/frequency of alcohol use and the score on the Michigan Alcohol Screening Test or MAST. A paternal history of alcohol or substance dependence (FHAOD) did predict ($\beta = 0.24$) Behavioral Undercontrol. Behavioral Undercontrol was also positively related ($\beta = 0.38$) to the Expectancies of Alcohol's Effects, but not to the age of first alcohol use. Measures of negative affectivity (PANAS, N-scale of the NEO) did not relate to a paternal history of alcoholism or to initiation of alcohol or other substance use.

At T2, these Time 1 SEM models were extended, using the T1 predictors of Behavioral Undercontrol and Conduct Problems to predict T2 alcohol and other substance use behaviors. Both Conduct Problems ($\beta = -0.21$ to 0.24) and Behavioral Undercontrol ($\beta = -0.21$–0.28) significantly predicted the individual ages of onset of tobacco, marijuana, and alcohol use. Again, negative affectivity was not a significant predictor of age of onset of any of these substances. By extending the model with respect to alcohol use, the T1 variables of Behavioral Undercontrol and Conduct Problems significantly predicted the age of first use of alcohol, which in turn predicted T2 Alcohol Problems ($\beta = -0.19$) as indicated by a subject's MAST score and frequency of alcohol use.

Data are still being collected at the T3 interval, so only preliminary findings are available. Based upon the currently available data set, T1 Conduct Problems ($\beta = 0.19$–0.27) and Negative Affectivity ($\beta = 0.22$–0.26) were significant predictors of Alcohol Problems at T3 as measured by the MAST, frequency of drinking, and severity of alcohol dependence as measured by Babor's Ethanol Dependence Scale. Behavioral Undercontrol was not a significant predictor of T3 Alcohol Problems as the majority of Behavioral Undercontrol's explanatory variance for T3 Alcohol Problems was carried by T1 Conduct Problems. T3 Social Support from family and friends did not predict T3 Alcohol Problems.

*Conclusions*. This longitudinal prospective study is beginning to provide an empirical test of the often-cited Deviance Proneness theoretical model describing possible pathways leading to pathological alcohol involvement and eventually into alcohol dependence. The findings presented suggest that the Deviance Proneness model is heuristically useful for longitudinal studies of alcohol use behavior, including alcohol problems. While many of the model's predicted relationships were supported, others were not. For example, the findings presented indicate that Deviance

**Table 1.** Sample Description

| | Time 1 | Time 2 | Time 3 |
|---|---|---|---|
| % Male | 43.8 | 40.6 | 40.2 |
| % Caucasian | 58.3 | 60.5 | 81.0 |
| % African American | 24.6 | 23.8 | 12.0 |
| %Hispanic | 24.6 | 23.8 | 7.0 |
| Age (years) | 16.5 ± .09 | 21.5 ± .10 | 26.1 ± 1.5 |
| % Single | 99.4 | 92.2 | 74.8 |
| Education (years) | 10.1 ± .01 | 13.4 ± .11 | 14.9 ± 1.8 |
| MAST | 2.5 ± 4.8 | 2.8 ± 5.7 | 3.9 ± 5.8 |
| *N* | 338 | 281 | 112 |

MAST, Michigan Alcohol Screening Test.

Proneness/Conduct Problems were consistent and sturdy predictors of alcohol use behavior and alcohol problems from early adolescence into young adulthood. Further, while Conduct Problems and Negative Affect were positively related, Negative Affect alone did not appear to directly influence the onset of first alcohol use. However, Negative Affect did influence the quantity and frequency of alcohol use once drinking behavior and drinking problems were established. Future analyses of this data set should further enhance our understanding of several putative risk factors that may contribute not just to the initiation of alcohol use, the maintenance of drinking behavior, and, in some individuals, drinking problems.

## AFFECT REGULATION AND ALCOHOL IN COGA: AN APPROACH USING SEM

*John R. Kramer and Kathleen K. Bucholz*

*Introduction*. Research has demonstrated that emotions or mood states are associated with increased alcohol involvement, ranging from daily intake among college students (Hussong et al., 2001) to heavy drinking (Rutledge and Sher, 2001) and serious drinking problems or diagnoses (Schuckit et al., 2005). Positive emotions typically have been found to increase drinking in social contexts, such as group celebrations. Negative emotions, in contrast, often have been associated with alcohol use in isolation. The present analyses examine 2 negative affective states, depression and anxiety, in relation to drinking. A number of other negative states that might play a role (e.g., anger, boredom) are not addressed here.

The associations observed between negative affect and drinking could be due to several mechanisms, either singly or in combination: First, drinking might reduce emotional turmoil and, through the mechanism of negative reinforcement, increase over time as a form of self-medication. This hypothesis is embedded in several related concepts, such as tension reduction (Conger, 1956; Greeley and Oei, 1999) and stress-response dampening (Croissant and Olbrich, 2004; Sher and Walitzer, 1986). However, at least among individuals with social phobia, the evidence that drinking actually reduces anxiety is not consistent (Carrigan and Randall, 2003). Second, even if negative emotions are not always alleviated by drinking, they might act as triggers (eliciting stimuli) to drink. That is, certain negative emotions might lead to an increase in drinking, either through learned or innate mechanisms. Third, negative emotions and drinking might be associated through other (third) variables. For example, a common set of genes might increase the risk of both negative affect and drinking (Merikangas et al., 1994). Fourth, drinking might lead to an increase in negative emotional states (e.g., depression), rather than the opposite. It is often difficult to discern the exact sequence of emotions and drinking, and a statistical association between the two could arise as a result of this "reverse" causality.

Sher's Negative Affect Vulnerability Model (Sher, 1991) provides a template for exploring relationships between negative affective states, drinking, and a variety of mediating and moderating variables. His model underscores the need to explore the relationship between negative affect and drinking through interactions with background influences (e.g., family drinking history), subject characteristics (e.g., temperament), and environmental circumstances (e.g., stress, peer relationships). This approach informed the present SEM analysis, which incorporates data from a large, collaborative national study on the genetics of alcoholism.

*Methods*. The COGA is a consortium of 7 research centers in California, Connecticut, Iowa, Indiana, Missouri, New York, and Washington, DC. The primary purpose of the project is to identify genes associated with alcohol dependence, abuse, and related phenotypes. The original COGA probands were ascertained through treatment centers and met the criteria for DSM-III-R Alcohol Dependence (American Psychiatric Association, 1987) as well as definite Feighner Alcoholism (Feighner et al., 1972). Subjects were required to speak English, to be free of extensive or recent intravenous drug use, and to have no life-threatening or incapacitating medical illness (except conditions that were alcohol-related). Additional details about ascertainment procedures can be found elsewhere (Begleiter et al., 1995). Information about psychiatric symptoms was collected through a reliable and valid interview, the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Bucholz et al., 1994; Hesselbrock et al., 1999).

The most genetically informative families were genotyped and followed up an average of 5 years later. Participants for the current analyses consisted of individuals drawn from nuclear and extended families of alcohol-dependent patients, focusing on those who were interviewed at 2 points in time. To be included, participants had to (a) be at least 18 years of age at the first assessment (Year 1); (b) have complete data on all variables used in the analysis; and (c) be relatives but not probands themselves, because the latter exhibited many comorbid conditions, making interpretation of results less straightforward. The resulting sample of 2,230 was 62% female, on average 43 years old (SD 12) at follow-up (Year 5), 79% Caucasian (19% African American; 2% other), with the majority (81%) having high school or some college education.

Mplus Structural Equation (Muthen and Muthen, 2004) was chosen as the statistical package to elucidate relationships among negative affect, drinking, and potential moderators and mediators. The latter were selected on the basis of findings from other studies as well as their availability in the COGA database.

*Manifest variables* selected for the analysis included: (a) Social Support from Family Members (obtained at Year 5 and based on a sum of 20 items, split at the median to indicate low social support; (Procidano and Heller, 1983);

(b) Family History of Alcoholism (DSM-III-R Dependence and Feighner Definite Alcoholism in mother and/or father); (c) Family History of Depression (DSM-IV lifetime diagnosis in mother and/or father); (d) Anxiety Symptoms [4 (Year 1) and 5 (Year 5) symptom count variables incorporating screening questions addressing agoraphobia, panic disorder, social anxiety disorder, OCD, and GAD (available at Year 5 only)]; and (e) Depression Symptoms (Years 1 and 5; count of 9 possible diagnostic symptoms arising during episodes that lasted at least 2 weeks and took place outside the context of heavy drinking). For both anxiety and depression, the symptom counts at Year 1 included lifetime occurrences; at Year 5, only symptoms that had arisen during the follow-up interval were included.

*Latent Variables* included (a) Alcohol Outcome [Years 1 and 5; symptom count scale including 7 dependence items, 4 abuse items, and 8 (Year 1) or 3 (Year 5) nondiagnostic items]. Symptom counts at Year 1 included lifetime occurrences; at Year 5, only symptoms that had arisen during the follow-up interval were included; and (b) Alcohol Expectancies (Brown et al., 1987; scales: Global Positive Changes, Sexual Enhancement, Physical and Social Pleasures, Increased Social Assertiveness, Relaxation/Tension Reduction, and Arousal/Aggression). The measurement model for latent variables was satisfactory, as assessed by Comparative Fit Index (CFI 0.978), Root Mean Square Error of Approximation (RMSEA 0.069), and Standardized Root Mean Square Residual (SRMR 0.023), supporting our choice of variables to represent the 2 domains.

*Results.* The model was initially conducted separately on females and males. Results were highly similar, suggesting no significant differences between the sexes, and all subjects were subsequently combined for the results discussed below.

Approximately one-third of the variance in alcohol symptoms at Year 5 was accounted for by the model. The best single predictor was alcohol symptoms at Year 1. This finding was not surprising, since past behavior often is the best predictor of future similar behavior.

On a *cross-sectional* basis, as anticipated, depression and anxiety symptoms assessed at Year 1 each were associated with alcohol symptoms at Year 1. Similarly, anxiety at Year 5 was associated with alcohol symptoms at Year 5. However, depression at Year 5 was negatively (counterintuitively) associated with alcohol symptoms at Year 5. This appeared to be an artifact of interactions (i.e., suppressor effects) in the full model, since the simple correlation between the two was not significant.

Regarding *longitudinal* analyses, neither depression nor anxiety at Year 1 was directly associated with alcohol symptoms at Year 5. However, simple correlations between both negative affective domains and alcohol were significant, suggesting that in the full model their associations operated through mediating variables. For example, anxiety at Year 1 was associated with Anxiety at Year 5, which predicted alcohol at Year 5. As another example, depression and anxiety at Year 1 each predicted alcohol symptoms at Year 1, which in turn predicted alcohol symptoms at Year 5.

In the model, the Family History of Alcoholism, Low Social Support, and Alcohol Expectancies each were positively associated with alcohol symptoms at Year 5, as hypothesized. At the same time, the family history of alcoholism and family history of depression were associated, possibly through assortative mating. However, a family history of alcoholism predicted subject alcohol symptoms at Years 1 and 5 but not subject depression at either year. Similarly, a family history of depression predicted subject depression symptoms at Year 1 but did not predict alcohol symptoms at either year. The lack of cross-disorder paths in the final model suggested that the biological bases for these 2 disorders did not overlap heavily.

*Conclusion.* These results provided some support for an association between negative affect, as measured by anxiety and depression symptoms, and increased risk for alcohol problems. Cross-sectional evidence was stronger than was longitudinal evidence. It is possible that the specific measurement instruments may have influenced the findings.

Future directions, all of which can be accomplished with current COGA data collection, include the following: (a) adding a third negative affective domain, irritability; (b) including not only alcohol-independent depression symptoms but also symptoms that occur within the context of heavy drinking; (c) including additional mediating and moderating variables, such as cognitive dysfunction, peer use, and high-risk alleles; (d) focusing on narrower age ranges, particularly younger adults who are closer in time to their symptom development; and (e) conducting follow-up assessments at shorter intervals (2 years rather than 5 years).

## DISCUSSION FOR THE SYMPOSIUM

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The papers represented here demonstrate the value of considering models of etiology and course that consider multiple influences at various stages of development. Each of the empirical presentations (Schuckit et al., Hesslebrock et al., and Kramer and Bucholz) attempts to model 1 of 3 posited etiological pathways to AUDs (Sher, 1991) that can invoke, to varying degrees, different explanatory constructs. These pathways can be assumed to work additively in conveying multifactorial influences. As noted by Windle, SEM allows a comprehensive approach to modeling that simultaneously addresses issues of measurement and structural relations among constructs. That is, SEM can evaluate the factor structure of a construct and take this into account in a structural model; can evaluate the reasonableness of measurement invariance in factor structure both across groups and over time; can model error structure of data; and can distinguish method and content

factors. Importantly, modern software packages offer various approaches to addressing questions of scaling of measures (a factor known to have significant effects on measures of fit and parameter estimates) as well as handle missing data (assuming certain assumptions can be met).

Turning to the issue of the modeling of structural relations across constructs, SEM can be used to evaluate the adequacy of various, alternative models. For longitudinal data, which are critical for testing etiological models, there is great flexibility in model-fitting approaches. For example, longitudinal data can be represented in a variety of ways including autoregressive processes (modeling the influence of prior status on later status), growth processes (modeling the starting point and slope of key constructs), and state-trait processes (e.g., decomposing a time-spanning process into more persistent or trait-like aspects and more situational or state-like aspects taking into account developmental aspects of the disorder). As we have argued elsewhere, state-trait approaches may be a particularly useful way of modeling alcohol dependence over the life course given what is known about its fluctuations over time as well as persistence. A major contribution of recent software developments is the ability to appropriately model continuous and categorical manifest and latent variables within a comprehensive modeling framework.

As noted by Windle, we must be ever mindful of the fact that correlational data are just that, ''correlational,'' and caution must be exercised when attempting to draw causal influences. Just because we are comprehensively modeling multiple constructs of interest does not mean we are carving nature at her joints, and that establishing causation can be very difficult and, in some cases, impossible. Fortunately, design features can, of course, help us to strengthen inferences, and longitudinal data (which can help establish temporal precedence or sequencing), genetically informative designs (which can help us identify common sources of influences), and instrumental variables (which can boost confidence in specifying a causal mechanism) can all help to refine our models and boost our confidence that causal mechanisms are being identified. A recent article by Caspi et al. (2005) elegantly illustrates the power of combining molecular genetic information with longitudinal data to characterize not only genetic and environmental risk factors but also the crucial nature of the timing of environmental exposures.

In SEM models in general and the papers presented here, a major threat to the validity of inferences is model misspecification. This can come about in 2 important ways, (1) misspecification of relations among modeled constructs and (2) misspecification by omitting key variables. Indeed, the latter is arguably the bane of correlational research, and there are many instructive examples [e.g., the failure to consider smoking in explaining the relation between platelet MAO and alcohol dependence (and other psychiatric disorders); the failure to consider levels and intensity of prior alcohol use and problems (especially when predicting categorical outcomes like DSM AUDs)].

There are many technical problems with modeling real-world data that researchers are only now beginning to tackle in earnest. Foremost among these are distributional problems. Observed data often do not behave well and often we do not have strong a priori rationales for how to scale/rescale. In alcohol data, a major problem is the issue of zero consumption. That is, the change from abstention to degree of use combines both a nominal component (nonuse to use) and a dimensional component (level of use). The problem generalizes to related phenomena such as ''problems'' or ''dependence symptoms'' and other alcohol-related ''count'' variables. Failure to distinguish abstention as a discrete category potentially confounds our view of the outcome. Fortunately, there are now approaches available for addressing this issue such as zero inflation models, but at present, they are rarely used in practice.

Although conducting the ideal study of alcoholism etiology remains an abstract goal, the studies presented here demonstrate some significant strengths that others conducting work in this area should consider. First, there is perhaps nothing more important than obtaining excellent follow-up rates in prospective studies and the follow-up success in the San Diego study is nothing short of remarkable. There is also great value in conducting multiple prospective tudies with different age cohorts to efficiently model life span developmental processes. Although a single, multiple cohort (also known as an accelerated longitudinal design) can sometimes be planned a priori, accessing multiple existing cohort studies represents another useful strategy. The measurement of theoretically relevant endophenotypes that can be presumed to be more proximal to core pathological processes (and genetic vulnerability) is also an important design feature that will probably also help us as we move more toward molecular genetic approaches and studying gene-environment interaction. The Hartford study illustrates the utility of richly assessing core constructs but the potential problems that can arise from high collinearity surrounding conceptually and empirically similar constructs. The study also illustrates the formidable challenges of attempting to maintain subject participation over long periods of time, a problem that many in the field are finding to be increasingly common. The Hartford study highlights the ostensibly different-looking pictures that often emerge from cross-sectional and longitudinal analyses of the same data and why it is critical to consider distinctions between etiological, escalating, and maintaining processes and the potential mediators of these effects.

Clearly, a complete picture of alcoholism etiology will require research that features many of components of the research presented in this symposium and that addresses multiple pathways, endophenotypic traits, sensitivity to developmental considerations, and a life course perspective. As noted by Windle, SEM is just a tool to help

us piece these parts of the puzzle together. How well we accomplish this will depend on the wisdom of our concepts and design, our ability to measure risk and protective processes, and our ability to use statistical tools to accurately represent them.

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