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Sex differences in how a low sensitivity to alcohol relates to later heavy drinking

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Abstract

Introduction and Aims—A low level of response (LR), or low sensitivity, to alcohol is a genetically-influenced characteristic that predicts future heavy drinking and alcohol problems. While previous analyses of how LR relates to heavier drinking reported the process is similar in males and females, some potential sex differences have been identified. This difference is further explored in these analyses.

Design and Methods—Prospective structural equation models (SEMs) were evaluated for 183 young adult females and 162 males, none of Asian background, from the Collaborative Study on the Genetics of Alcoholism (COGA). Invariance analyses and SEM evaluations by sex were used to compare across females and males for these primarily Caucasian (75%), non-Asian young (mean age 19) subjects.

Results—The prospective SEM for the full set of 345 subjects had good fit characteristics and explained 37% of the variance. While the initial invariance analyses identified few sex differences, comparisons of correlations and direct evaluations of path coefficients across males and females indicated that only females showed a link between a low LR and future alcohol problems that was partially mediated by more positive alcohol expectancies and drinking to cope. These sex differences were reflected in the different structures of the SEM results for female vs. male subjects.

Discussion and Conclusions—These prospective results indicate that there might be some important sex differences regarding how a lower LR relates to alcohol outcomes that should be considered in protocols focusing on preventing the impact of LR on future drinking problems.

Keywords

drinking; alcoholism; sex; genetics; structural equation models

Introduction

Factors that predispose people toward alcohol use disorders (AUDs) are heterogeneous, may operate differently in males and females, and involve both environmental and genetic components [1-3]. Such vulnerabilities include the low level of response (LR), or lower sensitivity, to alcohol [e.g., 4-6]. LR values are genetically influenced (e.g., they correlate higher in close relatives than in unrelated individuals and in identical compared to fraternal twins) [7, 8], and a low LR predicts future heavy drinking [9-11].

LR impacts on adverse alcohol outcomes both directly and through mediation by several additional characteristics. While few data are available to date on sex effects for these processes, overall it is hypothesized that: 1) people, especially during adolescence, tend to drink to obtain desired effects, such as intoxication; 2) those with low LR learn they need to consume relatively high amounts of alcohol to obtain the effects they want; 3) imbibing more alcohol per occasion in the context of a low LR contributes to selecting similar heavy drinking peers as friends [12]; 4) with repeated experience with alcohol, the low LR and the influence of heavier drinking peers alter what one expects to occur when drinking, and contributes to the belief that heavy drinking is normal behavior [13-15]; and 5) the resulting heavier drinking and associated behaviors increase life stresses which contribute to the use of alcohol to cope with stress [16]. These hypothesized relationships form the structure of the LR-based Structural Equation Models (SEMs) that have been well validated in male or combined male/female-based cross-sectional and prospective models [e.g., 6, 17-20].

However, few studies have thoroughly evaluated how males and females differ in the relationships among LR, potential mediators of the effect of LR of drinking (e.g., alcohol expectancies), and alcohol outcomes. This issue is relevant because there are multiple sex-related differences regarding drinking practices. For example, women tend to weigh less, have less muscle, and metabolize alcohol more slowly than men, and as a consequence develop a higher blood alcohol concentration (BAC) per drink (21-23). This greater effect per drink may be associated with their lower average consumption per drinking session and the finding that women are less likely to demonstrate most alcohol problems [23-29]. The two sexes might also differ on the impact that several of the components of the LR-based model might have on future drinking, thus potentially affecting how LR operates. This includes reports that females might be more responsive to peer pressures regarding alcohol consumption [1, 30, 31], may be more responsive to expectations of alcohol's effects on drinking patterns [32, 33], and may differ from males in their use of alcohol to deal with life stresses [27, 34].

SEM analyses have used a process called "invariance" (indicating a lack of difference across groups) within the SEM to determine if it was reasonable to combine the sexes in the analyses. However, determining that it is acceptable to combine males and females does not necessarily mean that the effects of LR in the two sexes are the same. Using a recent study as one of several possible examples, in an evaluation of a large sample of adolescents, invariance analyses indicated that males and females were similar enough to combine, even though the LR values were different across sexes, as were some relationships among the items used to measure some of the components of the model [19]. These and other results [e.g., 17, 18] indicated to us that it might be useful to more fully and directly explore potential male/female differences in the LR-based SEMs.

Therefore the current analyses take advantage of data available from a prospective study that included LR, potential mediators of the effect of LR, and alcohol-related outcomes. In this paper we evaluate the hypothesis that if separate LR-based models are tested for males and females, several of the mediators of outcomes incorporated in the model (e.g., expectancies) [30-33] might show greater effects related to how LR affects outcomes in females compared to males.

Methods

Subjects + Initial Interview

Using informed consent, data were obtained by following up 345 13-to-23-year-old offspring who had experience with alcohol from the Collaborative Study on the Genetics of Alcoholism (COGA) [18]. The COGA investigation began about 20 years ago with alcohol-dependent inpatients in substance disorder treatment programs who also had close relatives with alcohol dependence [18, 35, 36]. The current analyses focus on offspring from these families to evaluate sex differences in the LR-based model among adolescents and young adults at a time when alcohol use patterns are developing. All subjects were interviewed over ~one hour using the reliable (kappas ~0.85), and valid (kappas >0.72 compared to other structured interviews) Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) [35,36]. Outcomes were determined 2.2 (SD=0.64) years later through administration of an interval-focused SSAGA for ~80% of the subjects from Time 1.

Questionnaires at Time 1

LR was evaluated using the SRE (Cronbach α >0.90, and one-year retest reliabilities of .82) [11, 37]. Here subjects recorded the number of standard drinks (10 gm of ethanol) required early in their drinking careers for first feeling any effects of this drug, slurring speech, developing an unsteady gait, or unintentionally falling asleep, reporting only those effects actually experienced [4, 17-19]. The SRE score used here is the sum of number of drinks for the effects experienced the ~first five times of drinking (First 5), divided by the number of effects endorsed. Using the SRE, a greater number of drinks required for effects indicates a lower LR per drink consumed, a condition similar to the low LR scores generated from alcohol challenges [9, 11, 38-41].

Other Time 1 questionnaires relevant to the LR-based model included perceived drinking among peers (PEER) from the Important People and Activities Scale [42] regarding whether each of up to 12 close peers drinks, as well as their drinking frequencies and quantities (retest reliabilities >0.80, and good validity compared to other measures). Alcohol expectancies (EXPECT) were generated from age-appropriate Alcohol Expectancy Questionnaires (AEQ) (Cronbach α >0.7, retest reliabilities ~0.7, and good validities compared with comparable scales) [13, 43-45]. Using alcohol to cope with general life stress (COPE) was measured with the Drinking to Cope Scale (Cronbach α =0.85, and good validities and reliabilities) [46, 47].

SEMs

The maximum likelihood estimation for analysis of the variance/covariance matrix from the computer programs for Amos and Mplus were used to create measurement models and SEMs [48, 49]. LR was a manifest variable based on the weight-adjusted SRE, and alcohol outcome (ALCOUT) at Time 2 was a latent variable, or factor score, reflecting the usual maximum drinking quantity, as well as the quantities during the heaviest drinking week in the prior six months, along with as the number of 18 potential alcohol problems during the followup. PEER was a latent variable using the average drinking status among peers (using a

five-point scale from abstainer to heavier drinker), along with drinking frequencies and maximum quantities. Alcohol expectancies (EXPECT) used z-scores reflecting the age-appropriate AEQ values for Global Positive Expectancies, Social Behavior Expectations, Sex Enhancement, and Expected Relaxation Feelings. Finally, drinking to cope (COPE) was a latent variable made up of three indicators created after placing the six Drinking to Cope Scale items into three groups or parcels.

Steps were taken to evaluate if, in addition to a direct relationship between First-5 SRE and Time 2 alcohol outcomes, other Time 1 characteristics (e.g., peer drinking) also partially mediated how LR impacted on alcohol problems. For this, sequential multiple mediation pathways were evaluated using a product-of-coefficients test [50] within Mplus, version 5.1 [49] based on a bias-corrected bootstrap test (with 1000 resamples) [51], where at the lower (2.5) and upper (97.5) percentiles reflected the 95% confidence intervals, with mediation occurring if this interval does not include zero. The results of SEMs were evaluated through goodness-of-fit characteristics that included the comparative fit index (CFI) (good values >0.90), the non-normal fit index (NNFI) (good fit = values close to 1.0), the root mean square error of approximation (RMSEA) (good fit <0.05), and the root mean squared residual (SRMR) (good-fit <0.08) [52-54].

Comparisons across sexes included a sex-based invariance analysis as described by Hoyle and Smith [55] and Spillane et al. [56]. These involved adding, using a stepwise process, constraints for equal factor loadings across the sexes, then constraints for equal variance of exogenous variables, then for equality of correlations among indicators for latent variables, and finally constraints for equal path coefficients. Chi square was used to evaluate whether each constraint significantly decreased the model fit [52]. Also, to better understand sex differences in these models, the results for each sex were examined separately.

Results

Table 1 presents the characteristics for the 183 non-Asian females and 162 males used in these analyses, revealing no significant demographic differences. Time 1 alcohol and drug histories and SEM potential mediators (e.g., drinking to cope) were also generally similar across the sexes, except for higher maximum drinks, raw SRE scores (although the differences disappeared after adjusting for weight), and maximum peer drinking quantities, as well as more positive Global Positive Expectancies for males. At Time 2 males demonstrated higher drinking patterns and greater alcohol problems.

In preparation for the SEM analyses, Tables 2 and 3 present the correlations among weight-adjusted LR, outcomes, and their potential mediators for the full group, and for the two sexes separately. For the full sample in Table 2, LR at Time 1 was significantly related to alcohol outcomes at Time 2 and to Time 1 COPE, but was not significantly linked to the other SEM potential mediators. In contrast, all three potential mediators of the effect of LR on later outcome (peer drinking, alcohol expectancies, and drinking to cope) correlated significantly with Time 2 ALCOUT. Lower alcohol outcome scores were seen for females (male=1, female=2), and all three of the potential mediators were significantly related to each other. Older age at Time 1 related significantly only to more severe alcohol outcome scores. For Table 3, while females and males demonstrated similar correlations for most variables, there were several exceptions. These included the higher correlations in females for the relationship between LR and EXPECT ($z=2.41$, $p=0.02$ across males and females) and between LR and COPE ($z=2.71$, $p=0.01$), as well as lower correlations for females between age and ALCOUT ($z=-2.02$, $p=0.04$).

Figure 1 presents the results of the SEM (including the measurement model) for the combined sample of 345 males and females, with good fit indices as described in the legend. In Figure 1 the SEM explained 37% of the variance, and LR at Time 1 was connected to Time 2 outcome both directly and potentially through COPE. PEER and EXPECT were related to each other, and then to Time 2 outcomes indirectly through COPE. The SEM was not significantly impacted by age, and sex was only directly related to outcome, reflecting the more problematic alcohol outcomes for males. In this prospective model, mediation was seen for PEER through EXPECT through COPE to ALCOUT (confidence intervals: 0.419, 2.014), with the associated EXPECT through COPE to ALCOUT (0.070, 0.313), and PEER through COPE to ALCOUT (0.534, 2.892). However, the path from LR through COPE to ALCOUT was not quite significant (-.090, 2.090).

Potential sex differences in Figure 1 were further evaluated through an invariance procedure carried out in the SEM structure. In this approach the only significant chi square difference across steps was observed for correlations among indicators (or components) for latent variables ($\chi^2 [1] = 4.82, p=0.03$). No significant variation across sex was demonstrated for path estimates ($\chi^2 [7] = 7.30, p=0.40$), the variance of exogenous variables ($\chi^2 [2] = 0.71, p=0.71$), or for factor loadings ($\chi^2 [9] = 10.18, p=0.34$).

In light of the sex differences in correlations in Table 3 regarding the relationship of LR to potential mediators of outcomes, chi square was also used to directly evaluate potential differences across the path coefficients for LR to EXPECT and LR to COPE within the invariance analyses. Here, the path between LR and alcohol expectancies was significantly higher for females ($\chi^2 [1] = 4.30, p < 0.04$), with a trend for higher path values for the link between expectancies and coping (χ^2 difference [1] = 3.26, $p=0.08$). However, the sexes were not significantly different within the model for the LR to COPE path (χ^2 difference [1] = 1.39, $p=0.24$).

To further explore sex differences, separate SEMs (including measurement models) were evaluated for females and males, as shown in Figures 2 and 3. The SEM for females in Figure 2 explained 33% of the variance and the model for males in Figure 3 explained 24%. As shown in the figure legends, RMSEA was a bit lower for females (indicating a better fit), but the other fit characteristics were similar across the sexes. However, only the model for females demonstrated significant mediation of LR through EXPECT and COPE to ALCOUT (0.109, 2.102), and LR through EXPECT to COPE (0.093, 1.060). For males (Figure 3), LR was only directly linked to ALCOUT, without evidence of potential mediation. Both females and males showed mediation of PEER through EXPECT through COPE to ALCOUT (0.123, 2.161 and 0.316, 1.768, respectively).

Discussion

The major findings presented here relate to the different ways the effects of LR on alcohol outcomes might operate in females and males when their models were evaluated separately. These results occurred despite sex invariance in the SEM that indicated males and females were similar enough to combine in a single model. The separate sex-based SEMs were consistent with the fact that zero-order correlations of LR to EXPECT and LR to COPE in Table 3 were significantly different across the sexes, and that a direct comparison of LR-based models for males and females using invariance for Figure 1 indicated the LR to EXPECT path was significantly higher in females.

When two separate sex-specific models were created, only females demonstrated significant mediation of LR through EXPECT and COPE to ALCOUT. These results may reflect prior reports that women might be more sensitive to the impact of alcohol expectancies on

drinking practices [32, 33]. While not indicated in the prior literature [27, 34], the results might also support a greater meditational role for drinking to cope in females, at least within the LR-based model. However, the relationship of peer drinking to LR within the models was modest in both sexes, without evidence of mediation. In summary, the different rates of heavy drinking and alcohol problems in men and women might reflect, at least in part, the greater relationship of drinking in women to several mediators of the effect of a lower LR, as well as their higher overall LR per drink.

The differences between the sex-based invariance procedure for the full sample and the results from the separate analyses for males and females reflect the different issues the two statistical approaches address. If the question is whether the two sexes are enough alike to combine, then the similarities across males and females in how LR relates to outcomes, the way potential mediators in the models relate to each other and to outcomes, and the similar ways the indicators for most latent variables relate in the SEM components, all support the conclusion that in many ways the models for the two sexes are similar. However, if the question is whether there are *any* potentially interesting differences in how males and females perform in the model, with the emphasis of the question on what differences exist, there can be a different answer.

Our findings regarding sex-based differences might have some implications for approaches to diminish the risk for heavy drinking and alcohol problems in young drinkers. We recently demonstrated benefits of an LR-based prevention paradigm where subjects with a low LR showed significantly greater decreases in several alcohol-related adverse outcomes compared to low LR subjects who received the usual state-of-the-art approach to prevention [57]. The current results suggest that, in the future, optimal prevention sessions for males might place a greater emphasis on the direct impact of LR on adverse alcohol outcomes, while prevention protocols for females might also emphasize potential mediators of LR's effects, such as positive alcohol expectancies and using alcohol to cope with stress.

Finally, the results presented here must be viewed in light of the methods used. The COGA population is historically relatively blue collar in background and the original probands (e.g., grandparents or uncles of these offspring) came from families with a high prevalence of AUDs. Thus, the generalizability of the current results needs to be established through studies of other populations. Also, while the overall sample was fairly large (N=345), the sex-based analyses dealt with more modest-sized populations, a factor that could have impacted on results. Furthermore, while the LR measure used in these analyses was a retrospective questionnaire that related to a period about four years prior to the evaluation of PEER, EXPECT, and COPE, data about the early life LR were gathered at the same time as those potential mediators, and the follow-up to determine alcohol outcomes was only two to three years. It is important to determine whether different results would be observed with a longer-term fully prospective investigation. In addition, only one measure was used for each of the domains, including LR, and, to facilitate comparisons across sexes, the LR measure was considered after adjusting for weight. Finally, many additional sex-related differences may exist, but could not be explored in this relatively brief report focusing on the sex-related differences specifically within the LR-based model.

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References

- [1]. Kelly AB, Toumbourou JW, O'Flaherty M, et al. Family relationship quality and early alcohol use: evidence for sex-specific risk processes. *J Stud Alcohol Drugs*. 2011; 72:399–407. [PubMed: 21513676]
- [2]. Sher KJ, Grekin ER, Williams NA. The development of alcohol use disorders. *Annu Rev Clin Psychol*. 2005; 1:493–523. [PubMed: 17716097]
- [3]. Slutske WS, Heath AC, Madden PA, Bucholz KK, Statham DJ, Martin NG. Personality and the genetic risk for alcohol dependence. *J Abnorm Psychol*. 2002; 111:124–33. [PubMed: 11871377]
- [4]. Chung T, Martin C. Subjective stimulant and sedative effects of alcohol during early drinking experiences predict alcohol involvement in treated adolescents. *J Stud Alcohol Drugs*. 2009; 70:660–67. [PubMed: 19737489]
- [5]. Quinn PD, Fromme K. Subjective response to alcohol challenge: a quantitative review. *Alcohol Clin Exp Res*. 2011; 35:1759–70. [PubMed: 21777258]
- [6]. Schuckit MA, Smith TL, Anderson KG, Brown SA. Testing the level of response to alcohol: social information processing model of alcoholism risk--a 20-year prospective study. *Alcohol Clin Exp Res*. 2004; 28:1881–89. [PubMed: 15608605]
- [7]. Schuckit MA. An overview of genetic influences in alcoholism. *J Subst Abuse Treat*. 2009; 36:S5–14. [PubMed: 19062348]
- [8]. Vicken RJ, Rose RJ, Morzorati SL, Christian JC, Li T-K. Subjective intoxication in response to alcohol challenge: heritability and covariation with personality, breath alcohol level, and drinking history. *Alcohol Clin Exp Res*. 2003; 27:795–803. [PubMed: 12766624]
- [9]. Schuckit MA, Smith TL, Trim RS, Tolentino NJ, Hall SA. Comparing Structural Equation Models That Use Different Measures of the Level of Response to Alcohol. *Alcohol Clin Exp Res*. 2010; 34:861–68. [PubMed: 20201931]
- [10]. Trim RS, Schuckit MA, Smith TL. Predicting drinking onset with survival analysis in offspring from the San Diego prospective study. *Drug Alcohol Depend*. 2010; 107:215–20. [PubMed: 19959300]
- [11]. Schuckit MA, Smith TL, Trim R, Fukukura T, Allen R. The overlap in predicting alcohol outcome for two measures of the level of response to alcohol. *Alcohol Clin Exp Res*. 2009; 33:563–69. [PubMed: 19120060]
- [12]. Henry KL, Slater MD, Oetting ER. Alcohol use in early adolescence: the effect of changes in risk taking, perceived harm and friends' alcohol use. *J Stud Alcohol*. 2005; 66:275–83. [PubMed: 15957679]
- [13]. Bandura A. Self-efficacy: toward a unifying theory of behavioral change. *Psychol Rev*. 1977; 84:191–215. [PubMed: 847061]
- [14]. Dodge KA, Lansford JE, Burks VS, et al. Peer rejection and social information-processing factors in the development of aggressive behavior problems in children. *Child Dev*. 2003; 74:374–93. [PubMed: 12705561]
- [15]. Brown SA, McGue M, Maggs J, et al. A developmental perspective on alcohol and youths 16 to 20 years of age. *Pediatrics*. 2008; 121:S290–310. [PubMed: 18381495]
- [16]. Veenstra MY, Lemmens PH, Friesema IH, et al. Coping style mediates impact of stress on alcohol use: a prospective population-based study. *Addiction*. 2007; 102:1890–98. [PubMed: 18031425]

- [17]. Schuckit MA, Smith TL, Trim R, et al. The performance of elements of a 'level of response to alcohol'-based model of drinking behaviors in 13-year-olds. *Addiction*. 2008; 103:1786–92. [PubMed: 18778389]
- [18]. Schuckit MA, Smith TL, Danko GP, et al. An evaluation of the full level of response to alcohol model of heavy drinking and problems in COGA offspring. *J Stud Alcohol Drugs*. 2009; 70:436–45. [PubMed: 19371495]
- [19]. Schuckit MA, Smith TL, Heron J, et al. Testing a level of response to alcohol-based model of heavy drinking and alcohol problems in 1,905 17-year-olds. *Alcohol Clin Exp Res*. 2011; 35:1897–1904. [PubMed: 21762180]
- [20]. Schuckit MA, Smith TL, Trim RS, et al. A prospective evaluation of how a low level of response to alcohol predicts later heavy drinking and alcohol problems. *Am J Drug Alcohol Abuse*. 2011; 37:479–86. [PubMed: 21797810]
- [21]. Baraona E, Abittan CS, Dohmen K, et al. Sex differences in pharmacokinetics of alcohol. *Alcohol Clin Exp Res*. 2001; 25:502–07. [PubMed: 11329488]
- [22]. Eng MY, Schuckit MA, Smith TL. The level of response to alcohol in daughters of alcoholics and controls. *Drug Alcohol Depend*. 2005; 79:83–93. [PubMed: 15943947]
- [23]. Chermack ST, Stoltenberg SF, Fuller BE, Blow FC. Sex differences in the development of substance-related problems: the impact of family history of alcoholism, family history of violence and childhood conduct problems. *J Stud Alcohol*. 2000; 61:845–52. [PubMed: 11188490]
- [24]. Wilsnack RW, Vogeltanz ND, Wilsnack SC, et al. Sex differences in alcohol consumption and adverse drinking consequences: cross-cultural patterns. *Addiction*. 2000; 95:251–65. [PubMed: 10723854]
- [25]. Gruzza RA, Bucholz KK, Rice JP, Bierut LJ. Secular trends in the lifetime prevalence of alcohol dependence in the United States: a re-evaluation. *Alcohol Clin Exp Res*. 2008; 32:763–70. [PubMed: 18336633]
- [26]. Johnston, LD.; O'Malley, PM.; Bachman, JG.; Schulenberg, JE. Monitoring the Future national results on adolescent drug use: overview of key findings, 2010. Institute for Social Research, The University of Michigan; Ann Arbor: 2011.
- [27]. McCabe SE. Sex differences in collegiate risk factors for heavy episodic drinking. *J Stud Alcohol*. 2002; 63:49–56. [PubMed: 11925058]
- [28]. Nichol PE, Krueger RF, Iacono WG. Investigating sex differences in alcohol problems: a latent trait modeling approach. *Alcohol Clin Exp Res*. 2007; 31:783–94. [PubMed: 17386067]
- [29]. Wiesbeck GA. Sex-specific issues in alcoholism - introduction. *Arch Womens Ment Health*. 2003; 6:223–224. [PubMed: 14628172]
- [30]. Dick DM, Pagan JL, Viken R, Purcell S, Kaprio J, Pulkkinen L, Rose RJ. Changing environmental influences on substance use across development. *Twin Res Hum Genet*. 2007; 10:315–26. [PubMed: 17564520]
- [31]. Fowler T, Shelton K, Lifford K, Rice F, McBride A, Nikolov I, Neale MC, Harold G, Thapar A, van den Bree MB. Genetic and environmental influences on the relationship between peer alcohol use and own alcohol use in adolescents. *Addiction*. 2007; 102:894–903. [PubMed: 17523983]
- [32]. Agrawal A, Dick DM, Bucholz KK, Madden PA, Cooper ML, Sher KJ, Heath AC. Drinking expectancies and motives: a genetic study of young adult women. *Addiction*. 2007; 103:194–204. [PubMed: 18199298]
- [33]. Cable N, Sacker A. Typologies of alcohol consumption in adolescence: predictors and adult outcomes. *Alcohol Alcohol*. 2008; 43:81–90. [PubMed: 17934194]
- [34]. Patock-Peckham JA, Morgan-Lopez AA. Direct and mediational links between parental bonds and neglect, antisocial personality, reasons for drinking, alcohol use, and alcohol problems. *J Stud Alcohol Drugs*. 2010; 71:95–104. [PubMed: 20105419]
- [35]. Bucholz KK, Cadoret R, Cloninger CR, Dinwiddie SH, Hesselbrock VM, Nurnberger JI Jr, Reich T, Schmidt I, Schuckit MA. A new, semi-structured psychiatric interview for use in genetic linkage studies: a report on the reliability of the SSAGA. *J Stud Alcohol*. 1994; 55:149–58. [PubMed: 8189735]

- [36]. Hesselbrock M, Easton C, Bucholz KK, Schuckit M, Hesselbrock V. A validity study of the SSAGA--a comparison with the SCAN. *Addiction*. 1999; 94:1361–70. [PubMed: 10615721]
- [37]. Ray LA, Audette A, DiCristoforo S, Odell K, Kaiser A, Hutchison KE. Behavioral, laboratory, and genetic correlates of low level of response to alcohol. *Alcohol Clin Exp Res*. 2007; 31:131A.
- [38]. Chiu T-M, Mendelson JH, Sholar MB, Mutschler NH, Wines JD, Hesselbrock VM, Mello NK. Brain alcohol detectability in human subjects with and without a paternal history of alcoholism. *J Stud Alcohol*. 2004; 65:16–21. [PubMed: 15000499]
- [39]. Evans SM, Levin FR. Response to alcohol in females with a paternal history of alcoholism. *Psychopharmacology (Berl)*. 2003; 169:10–20. [PubMed: 12721780]
- [40]. Pollock VE, Teasdale TW, Gabrielli WF, Knop J. Subjective and objective measures of response to alcohol among young men at risk for alcoholism. *J Stud Alcohol*. 1986; 47:297–304. [PubMed: 3747531]
- [41]. Schuckit MA, Smith TL, Kalmijn J, Trim RS, Cesario E, Saunders G, Sanchez C, Campbell N. A comparison across two generations of prospective models of how the low level of response to alcohol impacts on alcohol outcomes. *J Stud Alcohol Drugs*. in press.
- [42]. Longabaugh R, Beattie M, Noel N, Stout R, Malloy P. The effect of social investment on treatment outcome. *J Stud Alcohol*. 1993; 54:465–78. [PubMed: 8341050]
- [43]. Brown SA, Christiansen BA, Goldman MS. The Alcohol Expectancy Questionnaire: an instrument for the assessment of adolescent and adult alcohol expectancies. *J Stud Alcohol*. 1987; 48:483–91. [PubMed: 3669677]
- [44]. Kline RB. Eight-month predictive validity and covariance structure of the Alcohol Expectancy Questionnaire for Adolescents (AEQ-A) for junior high school students. *J Stud Alcohol*. 1996; 57:396–405. [PubMed: 8776681]
- [45]. Schuckit MA, Smith TL, Trim R, Kreikebaum S, Hinga B, Allen R. Testing the level of response to alcohol-based model of heavy drinking and alcohol problems in offspring from the San Diego Prospective Study. *J Stud Alcohol Drugs*. 2008; 69:571–79. [PubMed: 18612573]
- [46]. Beseler CL, Aharonovich E, Keyes KM, Hasin DS. Adult transition from at-risk drinking to alcohol dependence: the relationship of family history and drinking motives. *Alcohol Clin Exp Res*. 2008; 32:607–16. [PubMed: 18341650]
- [47]. Cooper ML, Russell M, George WH. Coping, expectancies, and alcohol abuse: a test of social learning formulations. *J Abnorm Psychol*. 1988; 97:218–30. [PubMed: 3385075]
- [48]. Arbuckle, JL. Amos 18 User's Guide. SPSS, Inc.; Chicago: 2009.
- [49]. Muthén, LK.; Muthén, BO. Mplus User's Guide. Muthén and Muthén; Los Angeles: 2007.
- [50]. MacKinnon DP, Warsi G, Dwyer JH. A simulation study of mediated effect measures. *Multivariate Behavioral Research*. 1995; 30:41–62. [PubMed: 20157641]
- [51]. Fritz MS, MacKinnon DP. Required sample size to detect the mediated effect. *Psychological Science*. 2007; 18:233–39. [PubMed: 17444920]
- [52]. Bentler PM. Comparative fit indexes in structural models. *Psychol Bull*. 1990; 107:238–46. [PubMed: 2320703]
- [53]. Hu LT, Bentler PM. Fit indices in covariance structural analysis: sensitivity to underparametersized model misspecification. *Psychol Methods*. 1998; 3:424–53.
- [54]. Wheaton, B.; Muthén, B.; Alwin, DF.; Summers, GF. Assessing reliability and stability in panel models. Heise, DR., editor. *Sociology Methodology* Jossey-Bass; San Francisco: 1977. p. 84-136.
- [55]. Hoyle RH, Smith GT. Formulating clinical research hypotheses in structural equation models. *J Cons Clin Psychol*. 1994; 62:429–40.
- [56]. Spillane NS, Boerner LM, Anderson KG, Smith GT. Comparability of the eating disorder inventory-2 between men and women. *Assessment*. 2004; 11:85–93. [PubMed: 14994957]
- [57]. Schuckit MA, Kalmijn JA, Smith TL, Saunders G, Fromme K. Structuring a college alcohol prevention program on the low level of response to alcohol model: a pilot study. *Alcohol Clin Exp Res*. in press-a.

Figure 1.

The Structural Equation Model (with the Measurement Model included) for the full set of 345 subjects. Weight-adjusted level of response to alcohol (LR) and sex (SEX) are both manifest variables. Peer drinking (PEER) is a latent variable with indicators derived from the Important People and Activities Scale: *peera* = perceived peer status (from abstainer to heavy drinker), *peerb* = perceived peer drinking frequencies, *peerc* = perceived maximum drinking quantities. Alcohol expectancy (EXPECT) is a latent variable with indicators derived from the adolescent and adult Alcohol Expectancy Scales: *aeqg* = Global Positive Expectancies, *aeqs* = Social Behavior Expectancies, *aeqx* = Sex Enhancement, *aeqr* = Expected Relaxation feelings. Drinking to cope (COPE) is a latent variable with indicators derived from the 6 items of the Drinking to Cope scale with 2 items placed in each of 3 parcels: *dtca*, *dtcb*, *dtcc*. The outcome variable at Time 2 (ALCOUT) is a latent variable with indicators derived from questions regarding two quantities of drinking and the number of alcohol problems: *max* = maximum drinks in prior 6 months, *most* = maximum drinks during the heaviest drinking week in prior 6 months, *probs* = number of 18 potential alcohol problems during the followup. The significant path coefficients ($p < .05$) are presented for each path and the R^2 is provided for each latent variable including the final model R^2 which is given with the Time 2 alcohol outcomes (ALCOUT). Fit indices: CFI = .97, NNFI = .96, RMSEA = .052 (.040 - .064), SRMR = .054.

Figure 2.

The Structural Equation Model with the Measurement Model included for 183 females from Figure 2. See Figure 2 for domain and indicator descriptions. All shown relationships are significant. Fit indices: CFI = .99, NNFI = .99, RMSEA = .027 (.000 - .053), SRMR = .054.

Figure 3.

The Structural Equation Model with the Measurement Model included for 163 Males from Figure 2. See Figure 2 for domain and indicator descriptions. All shown relationships are significant. Fit indices: CFI = .96, NNFI = .95, RMSEA = .060 (.038 - .080), SRMR = .059.

Table 1

Comparison of 183 Females and 162 Males from COGA (means and sd or percents)

Variables (N)	All Ss (345)	Females (183)	Males (162)	χ^2/t -test
<u>Demography</u>				
Age (years)	19.1 (2.06)	19.2 (2.07)	19.0 (2.06)	0.68
Education (years)	12.0 (1.65)	12.2 (1.72)	11.9 (1.56)	1.82
Race (%)				
White	74.2	73.8	74.7	0.97
Hispanic White	13.0	12.0	14.2	
Black/Other	12.8	14.2	11.1	
Follow-Up interval (years)	2.2 (0.64)	2.2 (0.59)	2.3 (0.69)	-1.02
<u>Alcohol History Time 1</u>				
Age first drink	15.0 (2.24)	15.2 (1.86)	14.8 (2.59)	1.62
Days/week (6 mo)	1.1 (1.37)	1.1 (1.36)	1.2 (1.39)	-0.81
Drinks/drinking day(6 mo)	3.3 (4.16)	3.0 (3.87)	3.7 (4.46)	-1.44
Maximum Drinks Lifetime	14.3 (11.17)	12.1 (10.67)	16.8 (11.20)	-4.09 ^c
% Ever Problems	62.3	57.9	67.3	3.21
% Ever Abuse/Dependence	38.6	35.5	42.0	1.51
<u>Drug History Baseline (%)</u>				
Smoke	43.5	40.4	46.9	1.46
Marijuana	77.1	73.8	80.9	2.45
Cocaine	18.9	18.1	19.8	0.15
Amphetamine	13.1	11.0	15.4	1.49
<u>SEM Predictors</u>				
SRE (LR) *	3.5 (1.50)	3.2 (1.38)	3.9 (1.54)	-4.49 ^c
Weight-adjusted SRE	0.022 (0.01)	0.022 (0.01)	0.023 (0.01)	-0.58
PEER DRINKING *				
Drink Status	3.7 (0.96)	3.7 (0.95)	3.8 (0.98)	-0.53
Frequency	4.4 (1.97)	4.4 (2.02)	4.4 (1.91)	-0.31
Max Quantity	2.4 (1.32)	2.2 (1.32)	2.6 (1.31)	-2.26 ^a
EXPECTANCY *				
Global Positive	0.00 (1.00)	-0.12 (0.97)	0.13 (1.02)	-2.31 ^a
Social Behavior	0.00 (1.00)	-0.02 (0.95)	0.02 (1.05)	-0.35
Sexual Enhancement	0.00 (1.00)	-0.06 (1.06)	0.07 (0.92)	-1.26
Relaxation	0.00 (1.00)	-0.04 (1.02)	0.05 (0.97)	-0.79
COPE *				
Drink to Cope	10.2 (3.65)	10.1 (3.79)	10.3 (3.48)	-0.52
<u>Alcohol Variables Time 2</u>				
Days/week (6mo)	1.2 (1.48)	1.1 (1.47)	1.3 (1.48)	-1.12

Variables (N)	All Ss (345)	Females (183)	Males (162)	χ^2/t -test
Drinks/drinking day(6 mo)	3.1 (3.73)	2.6 (3.27)	3.7 (4.13)	-2.86 ^b
Maximum Drinks (6 mo)	9.2 (7.65)	6.8 (5.58)	11.9 (8.69)	-6.64 ^c
Most Drinks/drinking day in heaviest drinking week (6 mo)	4.9 (5.44)	4.0 (4.19)	6.0 (6.41)	-3.62 ^c
Number of 18 Problems	3.0 (3.28)	2.6 (3.22)	3.5 (3.30)	-2.44 ^a
% Problems	73.9	67.8	80.9	-7.65 ^b

* LR is the level of response to alcohol measured by the Self Report of the Effects of Alcohol questionnaire; PEER drinking is measured by the maximum peer score for each of the three Important People and Activities questionnaire items where peer frequency scale = 0 "none" to 7 "daily", peer max drinks scale = 0 "none" to 4 "10+", and drink status from 1 (abstinent) to 5 (heavy drinking) with 3 = light drinking; EXPECTANCY is measured by the scores on the Alcohol Expectancies Scale and z-scored within adult and adolescent versions; COPE is the score on the Drinking to Cope scale (note for COPE in the figures the 6 cope items placed into 3 parcels of 2 items each).

^a
p < .05

^b
p < .01

^c
p < .001

Table 2
Pearson Product Moment and Point Biserial Correlations for 183 COGA Female and 162 COGA Male Offspring

	LR		T2ALCOUT		PEER		EXPECT		COPE	
	F	M	F	M	F	M	F	M	F	M
Female/Male										
T2ALCOUT	.36 ^c	.26 ^a								
PEER	.07	-.06	.22 ^a	.25 ^a						
EXPECT	.18 ^a	-.08	.41 ^c	.23 ^a	.27 ^c	.26 ^b				
COPE	.25 ^b	-.04	.50 ^c	.40 ^b	.37 ^c	.40 ^c	.69 ^c	.63 ^c		
AGE	.07	-.02	.04	.26 ^a	-.07	.02	.03	.13	-.07	.14

^a = $p < .05$

^b = $p < .01$

^c = $p < .001$

T2ALCOUT = alcohol outcomes at Time 2 (max drinks 6 mos, most drinks during heaviest drinking week 6 mos, alcohol problems during followup); LR = SRE score (higher drinks needed for effects = lower LR per drink); PEER = perceived drinking status, frequency, and quantities of peers; EXPECT = scores on AEQ scales of global positive, social behavior, sex enhancement, and relaxation with alcohol; and COPE = scores on 3 parcels composed of 2 items each from the 6-item Drinking to Cope scale. In this Table, F indicates correlations among relevant variables for females, and M refers to correlations for males.

Table 3
Pearson Product Moment and Point Biserial Correlations for 183 COGA Female and 162 COGA Male Offspring

	LR		T2ALCOUT		PEER		EXPECT		COPE	
	F	M	F	M	F	M	F	M	F	M
Female/Male										
T2ALCOUT	.36 ^c	.26 ^a								
PEER	.07	-.06	.22 ^a	.25 ^a						
EXPECT	.18 ^a	-.08	.41 ^c	.23 ^a	.27 ^c	.26 ^b				
COPE	.25 ^b	-.04	.50 ^c	.40 ^b	.37 ^c	.40 ^c	.69 ^c	.63 ^c		
AGE	.07	-.02	.04	.26 ^a	-.07	.02	.03	.13	-.07	.14

Variables and p-values are as defined for Table 2. In this Table, F indicates correlations among relevant variables for females, and M refers to correlations for males.