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

MARC A. SCHUCKIT[1], TOM L. SMITH[1], RYAN S. TRIM[1,2], SAMUEL KUPERMAN[3], JOHN KRAMER[3], VICTOR HESSELBROCK[4], KATHLEEN K. BUCHOLZ[5], JOHN I. NURNBERGER JR[6], MICHIE HESSELBROCK[4] & GRETCHEN SAUNDERS[1]

[1]*Department of Psychiatry, University of California, San Diego, La Jolla, USA,* [2]*VA San Diego Healthcare System, San Diego, USA,* [3]*Division of Child Psychiatry, University of Iowa Hospitals, Iowa City, USA,* [4]*Department of Psychiatry, University of Connecticut Health Center, Farmington, USA,* [5]*Department of Psychiatry, Washington University, St. Louis, USA,* [6]*Institute of Psychiatric Research, Indiana University Medical Center, Indianapolis, USA*

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. 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 versus 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.* [Schuckit MA, Smith TL, Trim RS, Kuperman S, Kramer J, Hesselbrock V, Bucholz KK, Nurnberger Jr JI, Hesselbrock M, Saunders G. Sex differences in how a low sensitivity to alcohol relates to later heavy drinking. *Drug Alcohol Rev* 2012;31:871–880]

Key words: drinking, alcoholism, sex, genetics, structural equation models.

Introduction

Factors that predispose people towards alcohol use disorders 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].

Level of response impacts on adverse alcohol outcomes (ALCOUT) 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 hypothesised that: (i) people, especially during adolescence, tend to drink to obtain desired effects, such as intoxication; (ii) those with low LR learn they need to consume relatively high amounts of

Marc A. Schuckit MD, Professor of Psychiatry, Tom L. Smith PhD, Principal Statistician, Ryan S. Trim, PhD, Assistant Professor of Psychiatry, Samuel Kuperman MD, Professor of Child Psychiatry, John Kramer PhD, Professor of Psychiatry, Victor Hesselbrock PhD, Professor of Psychiatry, Kathleen K. Bucholz PhD, Professor of Psychiatry, John I. Nurnberger Jr. MD, Professor of Psychiatry, Michie Hesselbrock PhD, Professor of Psychiatry, Gretchen Saunders BA, Staff Research Associate. Correspondence to Dr Marc A. Schuckit, Department of Psychiatry, University of California, San Diego, 8950 Villa La Jolla Drive, Suite B-218, La Jolla, CA 92037, USA. Tel: +1 (858) 822 0880; Fax: +1 (858) 822 1002l; E-mail: mschuckit@ucsd.edu

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alcohol to obtain the effects they want; (iii) imbibing more alcohol per occasion in the context of a low LR contributes to selecting similar heavy drinking peers as friends [12]; (iv) 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 behaviour [13–15]; and (v) the resulting heavier drinking and associated behaviours increase life stresses which contribute to the use of alcohol to cope with stress [16]. These hypothesised 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 (EXPECT)] and ALCOUT. 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 metabolise alcohol more slowly than men, and as a consequence develop a higher blood alcohol concentration 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].

The 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 and 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 approximately 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 ~1 h using the reliable (kappas ~ 0.85), and valid (kappas > 0.72 compared to other structured interviews) Semi-Structured Assessment for the Genetics of Alcoholism [35,36]. Outcomes were determined 2.2 (SD = 0.64) years later through administration of an interval-focused Semi-Structured Assessment for the Genetics of Alcoholism for ~80% of the subjects from Time 1.

Questionnaires at Time 1

Level of response was evaluated using the Self-Report on the Effects of Alcohol (SRE) questionnaire (Cronbach $\alpha > 0.90$, and 1 year retest reliabilities of 0.82) [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). EXPECT were generated from age-appropriate Alcohol Expectancy Questionnaires (Cronbach $\alpha > 0.7$, 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 $\alpha = 0.85$, 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 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 6 months, along with as the number of 18 potential alcohol problems during the follow up. PEER was a latent variable using the average drinking status among peers (using a 5-point scale from abstainer to heavier drinker), along with drinking frequencies and maximum quantities. EXPECT used z-scores reflecting the age-appropriate Alcohol Expectancy Questionnaires 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 ALCOUT, 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 (good values >0.90), the non-normal fit index (good fit = values close to 1.0), the root mean square error of approximation (good fit <0.05) and the root mean squared residual (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. χ^2 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 ALCOUT 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, EXPECT and drinking to cope) correlated significantly with Time 2 ALCOUT. Lower ALCOUT 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 ALCOUT 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

Table 1. *Comparison of 183 females and 162 males from Collaborative Study on the Genetics of Alcoholism (means and SD or percentages)*

Variables (*n*)	All subjects (345)	Females (183)	Males (162)	χ^2/*t*-test
Demography				
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 (%)				0.97
White	74.2	73.8	74.7	
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
Alcohol history Time 1				
Age first drink	15.0 (2.24)	15.2 (1.86)	14.8 (2.59)	1.62
Days/week (6 months)	1.1 (1.37)	1.1 (1.36)	1.2 (1.39)	–0.81
Drinks/drinking day(6 months)	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
Drug history baseline (%)				
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
SEM predictors				
SRE (LR)[d]	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[d]				
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[d]				
Global positive	0.00 (1.00)	–0.12 (0.97)	0.13 (1.02)	–2.31[a]
Social behaviour	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[d]				
Drink to cope	10.2 (3.65)	10.1 (3.79)	10.3 (3.48)	–0.52
Alcohol variables Time 2				
Days/week (6 months)	1.2 (1.48)	1.1 (1.47)	1.3 (1.48)	–1.12
Drinks/drinking day(6 months)	3.1 (3.73)	2.6 (3.27)	3.7 (4.13)	–2.86[b]
Maximum drinks (6 months)	9.2 (7.65)	6.8 (5.58)	11.9 (8.69)	–6.64[c]
Most drinks/drinking day in heaviest drinking week (6 months)	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]

[a]$P < 0.05$, [b]$P < 0.01$, [c]$P < 0.001$. [d]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 six cope items placed into three parcels of two items each). SEM, structural equation model; SRE, Self-Report on the Effects of Alcohol questionnaire.

SEM was not significantly impacted by age, and sex was only directly related to outcome, reflecting the more problematic ALCOUT 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 (–0.090, 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 χ^2 difference across steps was observed for corre-

Table 2. *Pearson product moment and point biserial correlations for 183 COGA female and 162 COGA male offspring*

	LR		T2ALCOUT		PEER		EXPECT		COPE	
Female/male	F	M	F	M	F	M	F	M	F	M
T2ALCOUT	0.36[c]	0.26[a]								
PEER	0.07	–0.06	0.22[a]	0.25[a]						
EXPECT	0.18[a]	–0.08	0.41[c]	0.23[a]	0.27[c]	0.26[b]				
COPE	0.25[b]	–0.04	0.50[c]	0.40[b]	0.37[c]	0.40[c]	0.69[c]	0.63[c]		
AGE	0.07	–0.02	0.04	0.26[a]	–0.07	0.02	0.03	0.13	–0.07	0.14

[a]$P < 0.05$; [b]$P < 0.01$; [c]$P < 0.001$. In this Table, F indicates correlations among relevant variables for females, and M refers to correlations for males. AGE, age in years; COGA, Collaborative Study on the Genetics of Alcoholism; COPE, scores on three parcels composed of two items each from the six-item Drinking to Cope Scale; EXPECT, scores on Alcohol Expectancy Questionnaires scales of global positive, social behaviour, sex enhancement and relaxation with alcohol; PEER, perceived drinking status, frequency and quantities of peers; T2ALCOUT, alcohol outcomes at Time 2 (max drinks 6 months, most drinks during heaviest drinking week 6 months, alcohol problems during follow up); LR, SRE score (higher drinks needed for effects = lower LR per drink).

Table 3. *Pearson product moment and point biserial correlations for 183 COGA female and 162 COGA male offspring*

	LR		T2ALCOUT		PEER		EXPECT		COPE	
Female/male	F	M	F	M	F	M	F	M	F	M
T2ALCOUT	0.36[c]	0.26[a]								
PEER	0.07	–0.06	0.22[a]	0.25[a]						
EXPECT	0.18[a]	–0.08	0.41[c]	0.23[a]	0.27[c]	0.26[b]				
COPE	0.25[b]	–0.04	0.50[c]	0.40[b]	0.37[c]	0.40[c]	0.69[c]	0.63[c]		
AGE	0.07	–0.02	0.04	0.26[a]	–0.07	0.02	0.03	0.13	–0.07	0.14

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.

lations among indicators (or components) for latent variables (χ^2 [1] = 4.82, $P = 0.03$). No significant variation across sex was demonstrated for path estimates (χ^2 [7] = 7.30, $P = 0.40$), the variance of exogenous variables (χ^2 [2] = 0.71, $P = 0.71$) or for factor loadings (χ^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, χ^2 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 EXPECT was significantly higher for females (χ^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, the root mean square error of approximation 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 ALCOUT might operate in females and males when their models were evaluated separately. These results occurred despite sex invari-

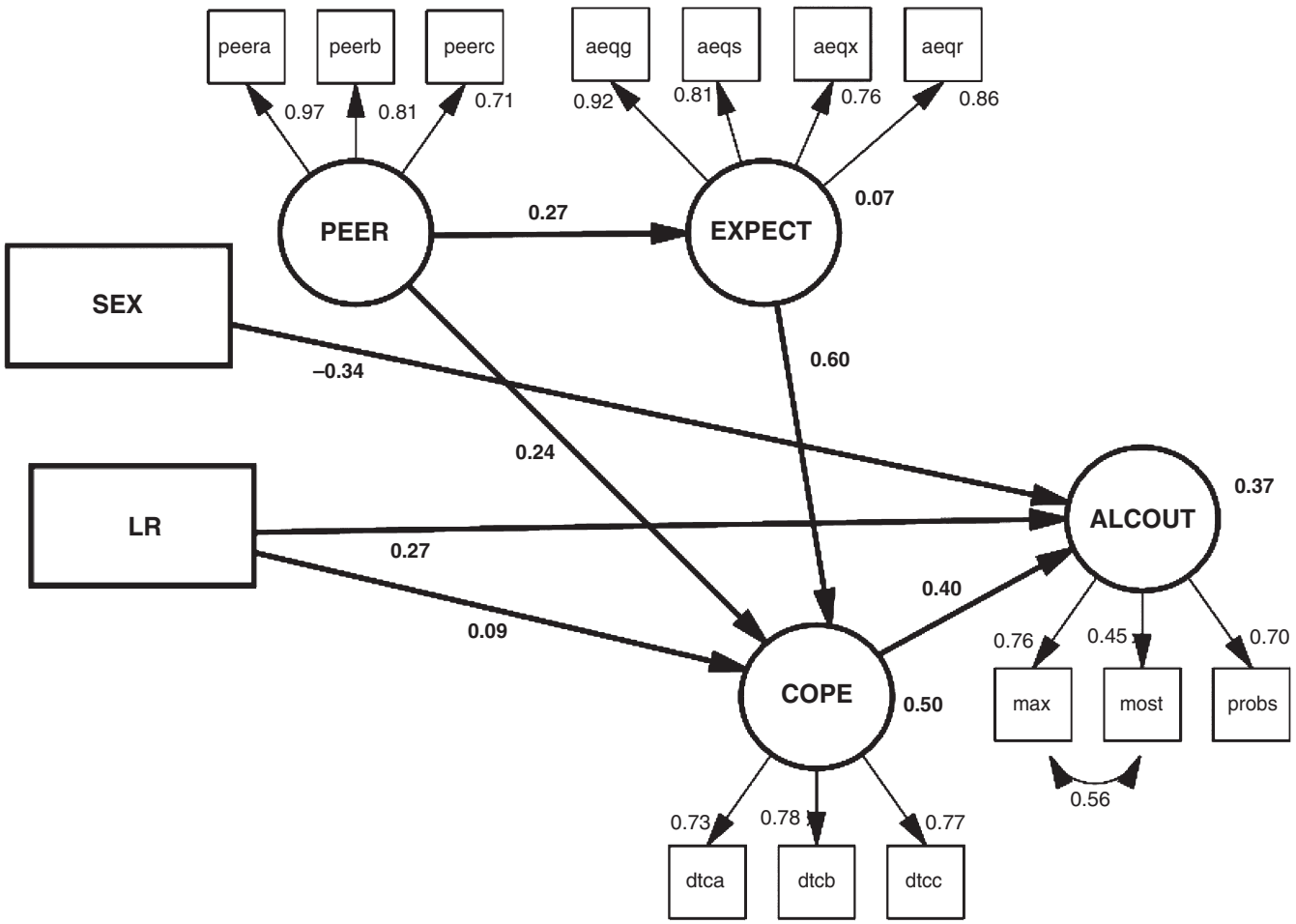

Figure 1. *The structural equation model (with the measurement model included) for the full set of 345 subjects. Weight-adjusted level of response to alcohol (LR) and sex (SEX) are both manifest variables. Peer drinking (PEER) is a latent variable with indicators derived from the Important People and 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 six items of the Drinking to Cope Scale with two items placed in each of three parcels: dtca, dtcb, dtcc. The alcohol 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 follow up. The significant path coefficients ($P < 0.05$) 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 ALCOUT. Fit indices: comparative fit index = 0.97, non-normal fit index = 0.96, root mean square error of approximation = 0.052 (0.040–0.064), root mean squared residual = 0.054.*

ance 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 EXPECT 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 the 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,

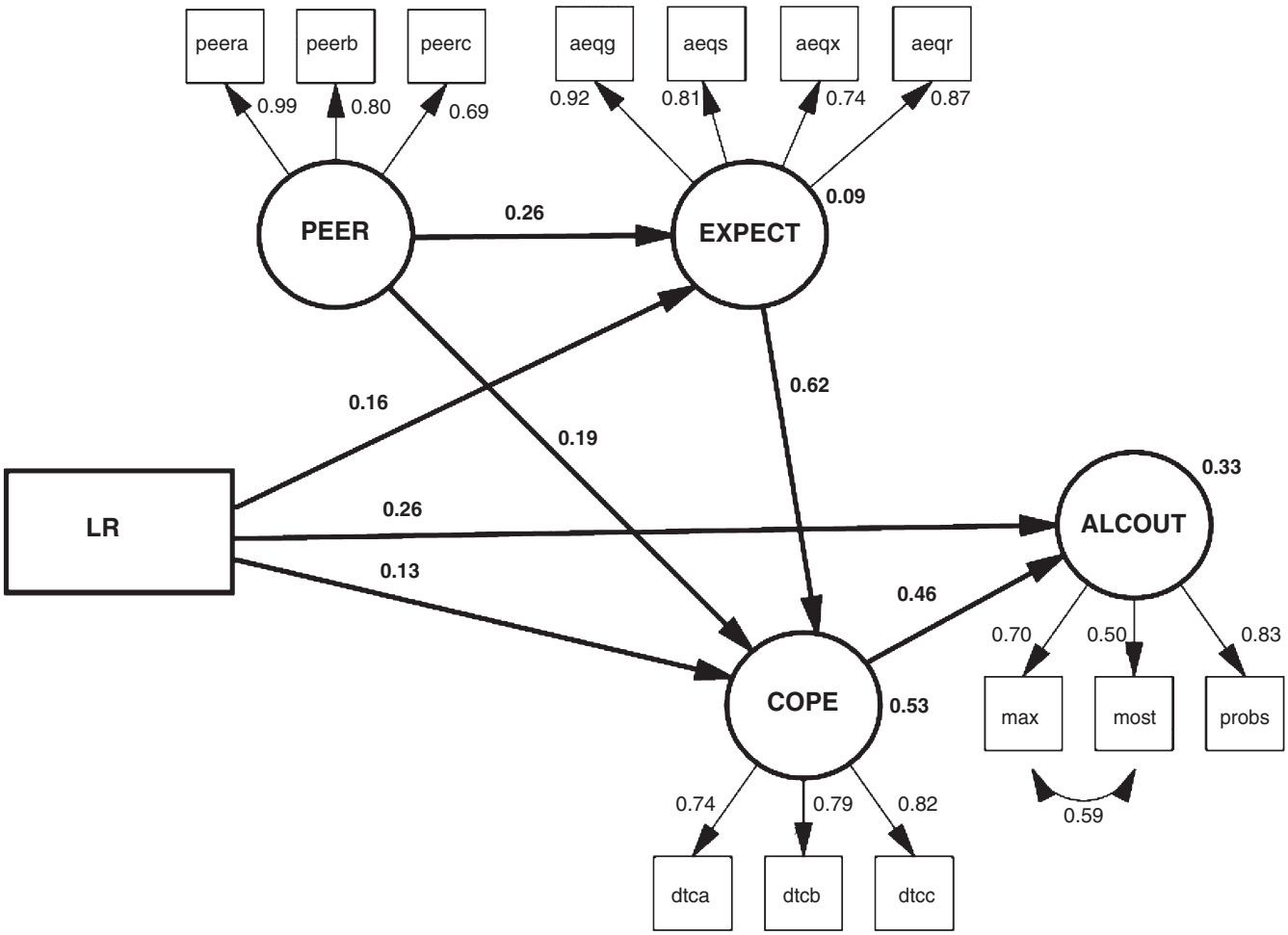

Figure 2. *The structural equation model with the measurement model included for 183 females from Figure 1. See Figure 1 for domain and indicator descriptions. All shown relationships are significant. Fit indices: comparative fit index = 0.99, non-normal fit index = 0.99, root mean square error of approximation = 0.027 (0.000–0.053), root mean squared residual = 0.054.*

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 ALCOUT, while prevention protocols for females might also emphasise potential mediators of LR's effects, such as positive EXPECT 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

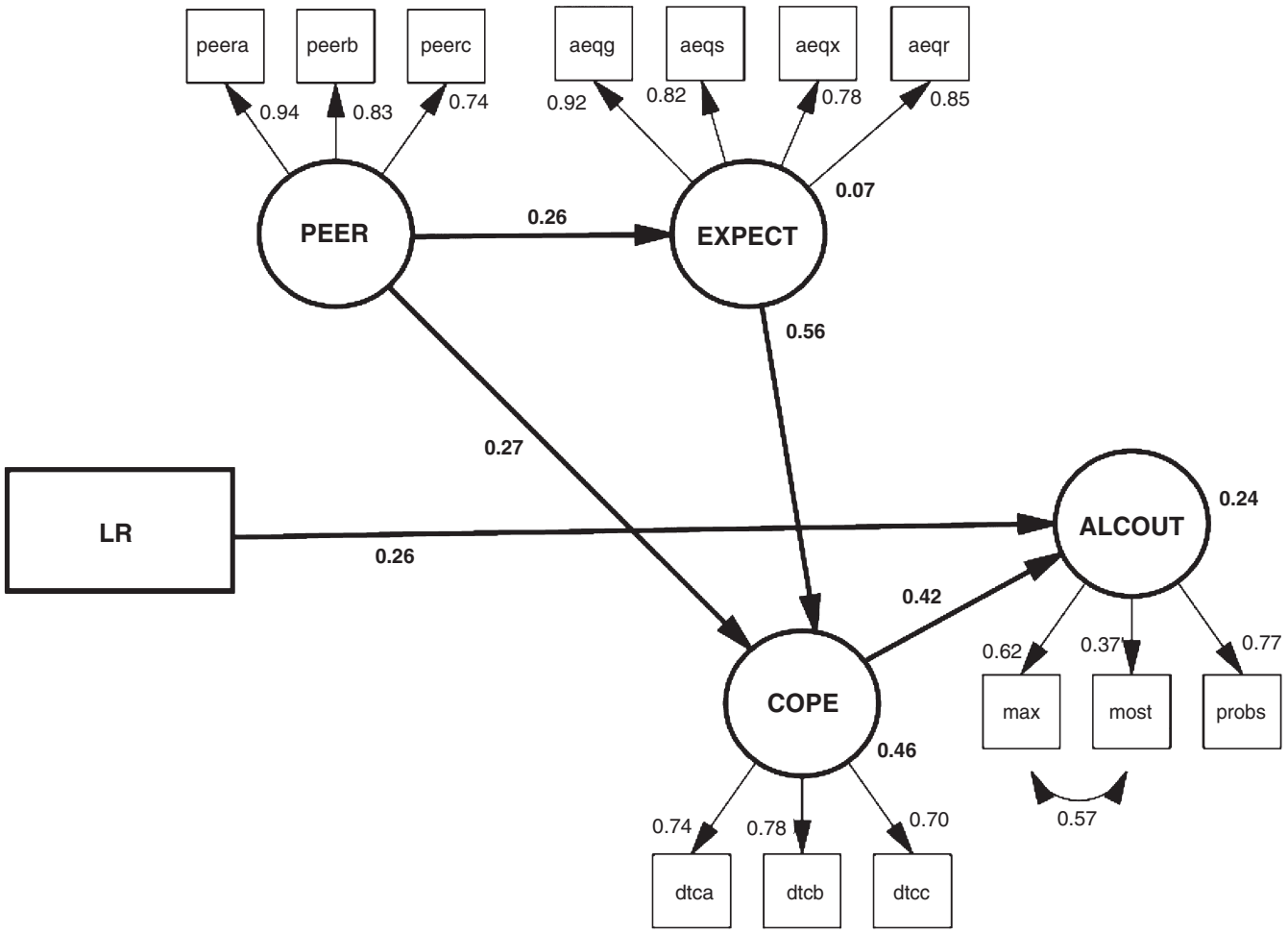

Figure 3. *The structural equation model with the measurement model included for 163 Males from Figure 1. See Figure 1 for domain and indicator descriptions. All shown relationships are significant. Fit indices: comparative fit index = 0.96, non-normal fit index = 0.95, root mean square error of approximation = 0.060 (0.038–0.080), root mean squared residual = 0.059.*

offspring) came from families with a high prevalence of alcohol use disorders. Thus, the generalisability 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 of approximately 4 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 ALCOUT was only 2–3 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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