The Ability of the Self-Rating of the Effects of Alcohol (SRE) Scale to Predict Alcohol-Related Outcomes Five Years Later*

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ABSTRACT. Objective: A low level of response (LR) to alcohol as measured through alcohol challenges is an early-appearing, genetically influenced characteristic that predicts the risk of heavier drinking and alcohol problems. A less expensive and more easily used measure of LR, the retrospective Self-Rating of the Effects of Alcohol (SRE) questionnaire, also relates to alcohol intake and problems but has not been evaluated for its ability to predict alcohol-related problems 5 years later. **Method:** At Time 1, 95 18- to 35-year-old (mean age: 25.9 years) subjects who were offspring from families participating at the San Diego site of the Collaborative Study on the Genetics of Alcoholism (COGA) were administered the SRE and evaluated regarding alcohol, drug, and demographic characteristics using the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) interview. Follow-up interviews (Time 2) using the SSAGA were completed an average (SD) of 5.4 (1.34) years later for approximately 80% of the original sample. **Results:** The retrospective SRE score at Time 1 (the number of drinks for effects the first five times [First 5] of drinking) correlated with Time 2 maximum quantity and frequency, alcohol problems overall, the number of alcohol-dependence items endorsed, and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, diagnosis of alcohol abuse or dependence. The relationships remained robust in hierarchical logistic regression analyses even in the context of age, gender, the number of SRE items endorsed, and alcohol use and problem variables at Time 1. The regressions explained between 21% and 43% of the variance of the outcomes overall, with the First 5 SRE score alone accounting for between 4% and 14%. **Conclusions:** These findings are consistent with the ability of SRE-based LR scores at Time 1 to predict alcohol-related outcomes over the subsequent 5 years. (*J. Stud. Alcohol Drugs* **68:** 371-378, 2007)

A LOW LEVEL OF RESPONSE (LR) TO ALCOHOL as measured on an alcohol challenge is an endophenotype associated with an enhanced risk of alcohol-use disorders (AUDs). Consistent with the criteria set forth by Gottesman and Gould (2003), the intensity with which a person responds to alcohol on these challenges is genetically influenced, with a heritability between 40% and 60% (Heath et al., 1999); low LRs are seen in individuals at elevated risk for AUDs (Ehlers et al., 1999; Eng et al., 2005; Schuckit and Smith, 2000); the lower response is apparent before alcohol dependence develops (King et al., 2006; Schuckit and Smith, 2000); and a low LR earlier in life is associated with an increased risk of later heavier drinking, alcohol problems, and AUDs (Heath et al., 1999; Rodriguez et al., 1993; Schuckit and Smith, 2000; Volavka et al., 1996). Structural equation models indicate that this endophenotype may contribute to consuming a higher number of drinks per occasion to achieve the desired effects, which might subsequently enhance the selection of heavier-drinking friends, alter what a person expects from alcohol, and enhance the probability that alcohol is used to deal with stress (Schuckit et al., 2004).

The classic evaluations of LR have used alcohol challenges to observe how subjects at high and low AUD risk responded to a standard dose of alcohol per kilogram at rising, peak, and falling blood alcohol concentrations (BACs). Measures have included alcohol-related changes in subjective feelings, motor performance, and physiological measures (Eng et al., 2005; Erblich and Earleywine, 1999; King et al., 2006; Pollock, 1992; Schuckit, 2002; Schuckit and Smith, 2000). However, these alcohol-challenge protocols are costly and time consuming and can be carried out only with healthy nonalcoholic individuals who are old enough to give informed consent (Schuckit, 2002; Wall et al., 1999). These constraints often result in data being gathered from relatively small samples with a limited range of demographic backgrounds.

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In an effort to overcome these restrictions, our group developed the 12-item Self-Rating of the Effects of Alcohol (SRE) questionnaire to evaluate the LR to alcohol early in life (Daeppen et al., 2000; Schuckit et al., 1997). Here, the LR is measured through the subject's recollection of the number of standard (~10 g of ethanol) drinks required early in the drinking career for up to four effects, including the amounts needed to first feel intoxicated, slur speech, create a stumbling gait, and cause a person to fall asleep when he or she did not wish to.

The most often used time frame for this questionnaire, the recall of drinks required for these effects for approximately the first five times of drinking (First 5), has good psychometric properties. The Cronbach α is .97, the 12-month retest reliability is as high as .8, and there is a significant relationship (as high as .6) of the SRE score to low and high extremes of LR established through alcohol challenges (Schuckit and Smith, 2004; Schuckit et al., 1997, 2001b, 2003b, 2005b,c).

The SRE score is familial and potentially genetically influenced, with significantly higher correlations for SRE values in close relatives compared with unrelated individuals (Schuckit et al., 2001a, 2005c). Evaluations of a relatively wide range of male and female subjects indicate that low LRs as measured by alcohol challenges or the SRE are associated with a higher cross-sectional maximum number of drinks consumed per occasion and with alcohol-related problems, even in subjects as young as 12 years who have only had limited experience with alcohol (Daeppen et al., 2000; Schuckit and Smith, 2000, 2004; Schuckit et al., 2001b, 2003b, 2005b, 2006b).

The highest cross-sectional and retrospective correlations between questionnaire-based LR and alcohol-related variables appear to be in younger subjects, perhaps because they are better able to remember their first several drinking experiences and because acquired tolerance was less likely to have developed and interfere with their memory of early alcohol effects (Schuckit et al., 2005a, 2006a,b).

In a recent evaluation of SRE-based LRs in 334 12- and 13-year-olds who had ever consumed at least one full drink, the early-life SRE score correlated with the maximum quantity of alcohol ever consumed at .49, ($p < .001$), alcohol-related problems at .28 ($p < .001$), and drinking frequency at .11 ($p < .05$) (Schuckit et al., 2006b). The correlations of SRE-based LR scores with drinking parameters remained significant even after controlling for variables that might themselves have related to alcohol-use patterns and problems, including the number of SRE items endorsed (as a measure of whether the overall SRE score was only a proxy for the types of experiences a person had early in his or her drinking career), weight (as heavier people require more drinks to have the same dose per kilogram as lighter individuals), age (because older teens might be expected to be more likely to drink more heavily and to have alcohol problems than younger subjects), and gender (as females have higher BACs per drink and because heavier drinking and alcohol problems are more common in males) (Breslin et al., 1997; Goist and Sutker, 1985; Whitfield et al., 1990).

For these 12- and 13-year-old subjects, the LR score from the SRE was not likely to reflect acquired tolerance, as the subjects had consumed alcohol an average of once per month over the prior 6 months, with approximately four being the maximum number of drinks ever consumed.

Thus, SRE-based LR values are familial and are seen in young subjects before alcoholism has developed. However, few studies have evaluated the third requirement for an endophenotype, the ability of SRE scores to predict future heavier drinking and alcohol-related problems. The current analyses address this question through a 5-year follow-up of subjects from the San Diego site of the Collaborative Study on the Genetics of Alcoholism (COGA).

Method

Subjects

The subjects were 18- to 35-year-old offspring from the San Diego site of the COGA study who gave informed consent to participate in the protocol (Bucholz et al., 1994; Schuckit et al., 2003a). As described in more detail elsewhere, COGA families were originally selected through a proband entering treatment for an AUD who met criteria for both Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R; American Psychiatric Association, 1987), alcohol dependence and definite alcoholism using the Feighner criteria (Bucholz et al., 1994; Feighner et al., 1972; Hesselbrock et al., 1999; Schuckit et al., 2001a, 2005b,c).

The COGA probands and their relatives came from families with multiple alcoholic relatives available for testing. Potential subjects were excluded if they did not speak English, could not cooperate in the interview, or had a life-threatening illness. Comparison families in San Diego were identified from among respondents to a questionnaire mailed to students and nonacademic staff at a university and were included regardless of the pattern of diagnoses in the family. The current sample is composed of 71 subjects from COGA pedigrees and 24 from comparison families.

Procedure

All COGA subjects and available first- and second-degree relatives were evaluated using the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) interviews (Bucholz et al., 1994; Hesselbrock et al., 1999). No participant used in the analyses had ever met criteria for alcohol dependence by the time of their first interview

(Time 1 [T1]), and approximately 80% of those eligible for follow-up were located and interviewed at Time 2 (T2). The data are limited to the San Diego group because this was the only COGA center to collect SRE forms routinely at T1 from all subjects who reported having experience with at least one full alcoholic drink.

The 18-35 age range was selected to include both younger subjects who reported a full drink and filled out the SRE and those along an upper age boundary beyond which alcohol dependence would be less likely to develop. Of course, age was used as a covariate in the regressions.

Analyses

The current evaluations focus on demography, alcohol use patterns, and SRE values at T1 as predictors of outcomes during the 5 years leading up to the T2 follow-up. The SRE data were extracted from the answers relating to the "first five times" a person ever drank alcohol for the following questions: (1) "How many drinks did it take you to begin to feel different?" (2) "How many drinks did it take you to begin to feel a bit dizzy, or begin to slur your speech?" (3) "How many drinks did it take you to begin stumbling, or walking in an uncoordinated manner?" and (4) "How many drinks did it take you to pass out, or fall asleep when you did not want to?"

Subjects were instructed to answer only for experiences they actually had in that time frame. The raw SRE scores for approximately the first five times of drinking (First 5) were generated by summing the drinks required for first feeling intoxicated, slurring of speech, stumbling gait, or unwanted falling asleep and dividing that figure by the number of effects endorsed (Schuckit et al., 1997).

For the current analyses, to evaluate the meaning of a person's SRE score relative to all other subjects who endorsed the same item, the value was generated through *z* scores among those who answered each SRE item, creating a sum of those *z* scores for each person, and dividing that corrected value by the number of items endorsed. This procedure yielded an assessment of the First 5 SRE that was independent of the number of items endorsed ($r = -.07$, $p = .48$). It should be noted that the raw scores (in addition to the *z* scores) performed similarly regarding the results reported in the Results section.

Outcomes during the 5-year interval (i.e., at T2) were extracted from the alcohol sections of the follow-up SSAGA, and T1 values for the same items were taken from the T1 SSAGA. The alcohol-related questions in that instrument have good reliability across different interviewers when evaluated 1 week apart, with overall κ's of .86 for continued use despite problems, .83 for withdrawal, .80 for tolerance, .77 for hazardous use, .74 for giving up activities, and so on, down to a low of .64 for using more alcohol than intended (Bucholz et al., 1994).

The sensitivity (92.3%), specificity (71.9%), and positive (64.9%) and negative (95.3%) predictive values for alcohol diagnoses from the SSAGA were established by comparison with the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) interview for 80 subjects (Hesselbrock et al., 1999). For the current analyses, the focus was placed on the maximum number of standard drinks (~10 g of ethanol) consumed on any occasion before T1 and in the 6 months before the T2 follow-up, the highest number of days of drinking per week over the prior 6 months at both T1 and T2, the number of the seven DSM-IV (American Psychiatric Association, 1994) dependence items endorsed as having occurred over the lifetime by T1 and during the 5 years before T2, and the number of 26 non-DSM alcohol problems ever reported by T1 and during the interval between T1 and T2 interviews. The non-DSM problems included items such as alcohol-related blackouts, drinking in the morning, alcohol-related arguments, and seeking help for alcohol-related problems.

The analyses described here are limited to white and white-Hispanic subjects for several reasons. First, prior studies using the SRE and alcohol challenges have usually been limited to these two groups (Daeppen et al., 2000; Schuckit et al., 2004, 2005c), and, therefore, these populations allow for more straightforward comparisons of current and past results. Second, these demographic groups represented 86% of the appropriate subjects participating in the San Diego COGA Center. Third, the rate of AUDs has been reported to be lower among black and Asian subjects than in white and Hispanic subjects (Hesselbrock et al., 2003; Li, 2000; Wagner et al., 2002; Wallace et al., 2003).

The relationships among variables were evaluated with the Pearson product moment statistic, using point biserial approaches when at least one of the variables (e.g., the outcome) was dichotomized. The dichotomized data were used to correct for any skew in distributions of any variable as would be seen with maximum drinks, alcohol problems, DSM outcomes, and so on.

The manner in which SRE and demographic items predicted each of the alcohol-related outcomes was then evaluated through hierarchical logistic regression analyses by entering all relevant variables (including age and gender as covariates) except for the First 5 SRE score on the first step, followed by the First 5 SRE value in the second step. (Note: Outcomes and T1 commensurate variables were dichotomized to correct for skewed distributions.)

The relevant table presents odds ratios, pseudo R^2s (an estimate of the proportion of the variance explained overall), and the change in R^2 when the SRE First 5 score was added as the second step in the regression. Although logistic regression is a nonparametric test evaluating likelihoods of "group membership," the amount of variance accounted for is most easily addressed through pseudo R^2s, and these reflect the computed likelihoods. In the context of the

dichotomous outcomes where, for example, the number of maximum drinks is presented as above or below the median to correct for skewed distributions, the logistic regression actually indicates the probability of maximum drinks being higher than the median.

Results

The 95 San Diego COGA study relatives reported here represent all available 18- to 35-year-old white individuals who filled out the SRE at T1 and who participated in the follow-up interview (T2) an average (SD) of 5.4 (1.34) years later. These include 36 men (37.9%), and at T1 the mean age for the entire group was 25.9 (5.68) years. Table 1 presents the demographic and alcohol-related patterns at T1 as well as outcomes over the 5 years for the 95 subjects.

Although not shown in the table, the two genders were generally similar at T1 and T2, except for the expected overall heavier drinking pattern and higher SRE scores for men. For this sample, although the age referred to for the First 5 SRE question was not specifically recorded, the age of onset of more regular drinking (i.e., at least once per month for 6 months) was 17.3 (2.61) years.

In Table 1, for relevant variables (e.g., number of alcohol problems), the mean data include zeros. Reflecting the skewed distribution of some outcome scores, to facilitate appropriate approaches to regressions, maximum quantity and frequency were treated as a dichotomy of below the median versus at or above the median, whereas the two alcohol problem scores and AUD diagnoses were scored as zero versus greater than zero.

Demographic characteristics and alcohol-related items at T1 for the 95 subjects in this report were similar to additional eligible subjects who did not participate in the follow-up for education, First 5 SRE, maximum drinks in a lifetime, maximum frequency per week, number of alcohol problems, and alcohol diagnosis, but the subjects who were successfully followed were about 5 years older and more likely to be female and married.

Table 2 presents correlations among the two SRE variables and demography from T1 and the five alcohol-related outcomes at T2. At T1 the *z* score-generated First 5 SRE scores correlated significantly with gender (lower scores indicating less alcohol needed for effects for women), but this SRE value did not correlate with age or number of SRE items endorsed. The First 5 value also correlated positively and significantly with all five alcohol-related outcomes, where more drinks required for effects early in life related to more drinking and more problems at T2.

It is important to note that more drinks needed for effects on the SRE indicates less effect per drink or a lower LR. In contrast to the SRE score, the number of items endorsed did not correlate significantly with demography or with any T2 variable. All outcomes were correlated with each other, and whereas gender related with outcomes of frequency, non-DSM problems, and diagnoses, age correlated with quantity, problems, the number of dependence items endorsed, and diagnoses.

Although not shown in the table, each T2 outcome was also evaluated for its relationship to a similar item at T1, with correlations across T1 and T2 of .19 ($p = .08$) for quantity, .36 ($p < .001$) for frequency, .07 ($p = .53$) for the 26 problems, and .16 ($p < .12$) for the number of dependence items. Although, by definition, no subject met criteria for alcohol dependence at T1, if the endorsement of any abuse item before T1 was considered, the correlation of such a history at T1 with alcohol abuse or dependence at T2 was .16 ($p = .13$).

Table 3 presents the results of five hierarchical logistic regressions using T1 SRE and demography to predict the probability, or odds, of higher T2 alcohol-related outcomes, while considering the respective corresponding T1 values for each outcome measure. Thus, the equation predicting the probability of the maximum drinks at T2 falling above

TABLE 1. Demographic characteristics, SRE, alcohol outcomes at Time 1, and alcohol outcomes at Time 2 for 95 subjects

Demography		Time 1 variables		Time 2 outcomes	
Age, mean (SD)	25.9 (5.68)	SRE, mean (SD)	2.8 (1.17)	Maximum drinks 6 months, mean (SD)	3.4 (3.53)
Education in years, mean (SD)	13.7 (1.76)	No. of SRE items endorsed, mean (SD)	2.8 (0.83)	Maximum frequency/week prior 6 months, mean (SD)	1.7 (1.83)
Religion, %		Endorsed SRE Item 1, %	100	No. of alcohol problems (of 26), mean (SD)	0.90 (1.83)
Protestant	49.5	Item 2	89.5	No. of DSM-IV items, mean (SD)	0.31 (0.77)
Catholic	31.6	Item 3	73.7	Alcohol diagnosis, %	29.5
No religious affiliation	16.8	Item 4	14.7	Dependence	4.2
Other religions	2.1	Maximum drinks lifetime, mean (SD)	11.0 (8.25)	Abuse	25.3
Marital status, %		Maximum frequency/week prior 6 months, mean (SD)	1.1 (1.42)		
Married	54.7	No. of alcohol problems (of 26) lifetime, mean (SD)	2.1 (2.09)		
Separated/divorced	7.4	No. of DSM-IV items lifetime, mean (SD)	0.5 (0.75)		
Never married	37.9				

Notes: SRE = Self-Rating of the Effects of Alcohol; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.

TABLE 2. Correlations among SRE variables at Time 1 and alcohol outcomes at Time 2 for 95 white and Hispanic subjects

Variable	*z* score first 5 SRE	No. of Items endorsed	Age	Gender	Maximum quantity	Maximum frequency	No. of 26 problems	No. of 7 DSM-IV dependence items
Predictors, Time 1								
No. of items endorsed	-.07							
Age	.14	.13						
Gender	-.35‡	-.05	.00					
Outcomes, Time 2								
Maximum quantity	.22*	.12	-.24*	-.10				
Maximum frequency	.26*	.15	-.08	-.24†	.62‡			
No. of 26 problems	.28†	.02	-.39‡	-.30†	.52‡	.44‡		
No. of 7 DSM-IV dependence items	.25*	.07	-.25*	-.12	.36‡	.32†	.52‡	
Alcohol diagnosis	.30†	.03	-.29†	-.26†	.51‡	.47‡	.85‡	.51‡

Notes: SRE = Self-Rating of the Effects of Alcohol; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders.
*$p < .05$; †$p < .01$; ‡$p < .001$.

the median incorporated T1 maximum drinks as a predictor, the regression predicting a T2 frequency above the median incorporated T1 maximum frequency, and so on. These are listed as "respective corresponding measures at Time 1" in the columns in Table 3.

For each equation, the proportion of the variance explained overall is listed on the second line from the bottom, and the R^2 change (reporting the proportion of variance added uniquely by the *z* score-based SRE score) is at the bottom of each column. The table reveals that the SRE score contributed significantly to the overall equation for the prediction of four of the outcomes. The exception was maximum frequency, where the odds ratio for the SRE score was 1.82 ($p = .06$), and the R^2 change was .04 ($p = .06$). By contrast, the number of SRE items endorsed did not add significantly to any regression.

Regarding the respective corresponding measure at T1, only T1 frequency—but not prior quantity or problems—added to the regression predicting that outcome. Among the remaining predictors, only age contributed significantly to more than one equation and gender contributed only to predicting the 26 problems. Overall, pseudo R^2s were between .21 and .43, and the R^2 change added by the SRE ranged from .04 to .14.

Two additional analyses were carried out to further clarify the results in Table 3. As noted earlier, although no subject had been alcohol dependent at T1 (and, thus, none were original COGA probands), 24 of the 95 individuals came from comparison families and 71 from pedigrees related to the original COGA alcohol-dependent subject. Thus, the regressions in Table 3 were repeated but now had added to them the comparison group versus COGA family status as a predictor.

This step yielded results very similar to those presented in Table 3, with no significant contribution from the subject source (e.g., comparison family) variable, no new items reaching significance, only one significant item from Table 3 dropping out (gender predicting 26 problems), and with the proportions of the variances explained remaining virtually unchanged.

Finally, despite the skewed nature of the distribution of the outcome variables, the analyses in Tables 2 and 3 were

TABLE 3. Hierarchical logistic regression analyses predicting the probability or odds ratios and pseudo R^2s for five Time 2 outcomes ($N = 95$)[a]

Predictors	Maximum quantity	Maximum frequency	No. of 26 problems	No. of 7 DSM-IV dependence items	Alcohol diagnosis
z score first 5 SRE	1.99*	1.82	2.76†	3.51†	2.85†
No. of items endorsed	1.67	1.67	1.23	1.71	1.26
Respective corresponding measures at Time 1	1.32	4.17†	1.43	1.76	1.21
Age	0.88†	0.93	0.78‡	0.81†	0.82‡
Gender	1.07	0.59	0.32*	1.34	0.51
Pseudo R^2	.21†	.23†	.43‡	.30†	.36‡
R^2 change for first 5 SRE	.06*	.04	.08†	.14†	.11†

Notes: SRE = Self-Rating of the Effects of Alcohol; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. [a]Although logistic regression is nonparametric, the amount of variance accounted for is more easily presented using pseudo R^2s. However, the *p* values reported for the R^2s are actually those for the likelihood ratio tests.
*$p < .05$; †$p < .01$; ‡$p < .001$.

repeated using the raw data for all continuous variables, with results very similar to those reported earlier using dichotomous variables.

Discussion

This is the first study known to the authors to establish the ability of SRE-based LR scores to predict a range of alcohol-related outcomes 5 years later. In our analyses, the SRE value correlated with future drinking quantity and frequency, two measures of alcohol-related problems, and AUDs. As shown in Table 3 and the text, the findings remained robust after controlling for the number of SRE items endorsed, relevant drinking patterns and problems at T1, and the type of family from which the subjects came.

The consistency of the findings across outcomes underscores the potential clinical utility of the SRE as a predictor of problems above and beyond gender, age, and T1 alcohol use and problems. These results are consistent with the conclusion that these questionnaire-generated LR scores may fulfill criteria for an endophenotype (Gottesman and Gould, 2003), as the SRE scores are familial (Schuckit et al., 2001a, 2005c) and potentially genetically influenced, low LR scores (i.e., high SRE values) are noted before alcoholism develops (Schuckit et al., 2005a, 2006b), and the current results indicate that SRE-based LR scores predict future heavier drinking and alcohol problems.

Using simple correlations, the First 5 SRE score related significantly to all five outcomes. In the regressions and after incorporating T1 drinking patterns and problems as predictors, the SRE score continued to predict four outcomes and was associated with significant changes in the R^2 for these variables.

The only exception was for maximum frequency of drinking at T2, and even here the odds ratio for the SRE in the regression and the R^2 change approached significance ($p = .06$). The potential for a less robust performance for the SRE score regarding frequency is consistent with the theory that LR may impact most directly on how much a person drinks on an occasion, as they may consume alcohol until the desired effects are achieved, but LR might have little direct impact on how often a person drinks (Schuckit, 2002; Schuckit et al., 2006b).

The subjects evaluated here consisted of both men and women and included a modest age range. Regarding gender, although both sons and daughters of alcoholics have been shown to demonstrate a lower LR than controls (Eng et al., 2005; Evans and Levin, 2003; Lex et al., 1988; Schuckit et al., 2000), the literature also supports a lower number of drinks required for effects for women compared with men overall.

Women are expected to demonstrate higher BACs than men after a given number of drinks because of their usual lower body weight and also to show higher BACs based on drinks per kilogram as a reflection of their less efficient first-pass metabolism of alcohol in the esophagus and stomach as well as their expected lower proportion of body water (Breslin et al., 1997; Goist and Sutker, 1985; Whitfield et al., 1990). Thus, the negative correlation between gender and the SRE score in Table 2 may reflect a lower number of drinks for effects for women.

However, gender added significantly to only one of the regressions, and the SRE score remained significant as a predictor of outcome in a sample composed of both men and women. Age was not related to any other predictor in Table 2 and demonstrated a negative correlation with four of the five outcomes. However, in Table 3, the relationship between the SRE score and alcohol-related outcomes remained robust even after including age in the regression analyses.

The proportions of the variance of outcomes (i.e., pseudo R^2s) reported for the five regressions in Table 3 were modest, ranging from 21% to 43%. The R^2 change, reflecting the proportions of variance of outcomes independently accounted for by the First 5 score, ranged from 4% to 14% across outcomes.

These findings underscore the complex and multifactorial nature of alcohol-related outcomes, where multiple endophenotypes and a range of biological, social, and cultural factors combine to contribute to the alcohol-related behaviors (McGue, 1997; Schuckit, 2002; Schuckit et al., 2004). Indeed, even when structural equation models incorporating multiple domains of outcomes are used, rarely more than 50% of the variance can be explained (Schuckit et al., 2006a).

Despite the performance of the SRE in the current analyses and in recent studies (Schuckit et al., 2006b), it is important to remember that the data regarding the prognostic implications and genetic influences regarding LR as determined with this questionnaire are more limited than those available from the alcohol challenges. In addition, there are important differences between the two types of evaluations.

In contrast to laboratory measures of LR, the SRE is retrospective; all items involve recollections of subjective effects; it is difficult to correct results for height, age, and weight during the First 5 period; there are no corroborating observations of LR; and it is not possible to compare effects at rising versus falling BACs.

At the same time, alcohol challenges are expensive and cannot be used in very young, older, or ill subjects but do give detailed evaluations of multiple aspects of LR. Also, this is the only study to evaluate the prognostic implications of the SRE-generated LR score, although at least four investigations have shown alcohol-challenge LRs do predict outcomes (Heath et al., 1999; Rodriguez et al., 1993; Schuckit and Smith, 2000; Volavka et al., 1996). Thus, alcohol challenges might still be considered the "gold standard" measures of LR for all types of studies, including genetic analyses.

Although the possible mechanisms through which LR may enhance heavier drinking and related problems have been evaluated in several studies (Schuckit and Smith, 2000; Schuckit et al., 2004, 2005b), additional mediators might operate. For example, both a lower LR and adverse alcohol outcomes could reflect drinking early in life to enhance more positive effects of alcohol. Also, whereas the alcohol challenges might avoid this problem, establishing LR through the retrospective SRE could reflect a recall bias regarding early effects of alcohol among subjects who are heavier drinkers at both T1 and T2.

Additional caveats regarding the current study should be noted. The sample size is somewhat small, the COGA protocol was relatively restrictive in how the original probands had been selected from alcohol treatment programs, data were only analyzed here regarding white (including white-Hispanic) subjects from one COGA center, and no data were available on other racial and ethnic groups.

Furthermore, to correct the skew in distribution for several of the outcomes, all five such T2 variables were dichotomized and logistic regressions were used, although the results were similar when continuous variables were substituted in the analyses. In addition, to optimize ease of use and scoring, the SRE lists effects without weighing the scores on a scale from less to more severe effects.

Thus, the current results must be considered preliminary until additional follow-up studies are carried out using additional aspects of the SRE as a measure of LR. Finally, the estimated follow-up rate of about 80% over 5 years is quite good but didn't reach the 20-year rate of greater than 95% of some other studies (Schuckit et al., 2004). The lower figure for COGA reflects the much larger sample overall, along with financial constraints that did not allow the more intense and time-consuming follow-up approaches used in the other San Diego Prospective Study.

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