Developing a Quantitative Measure of Alcohol Consumption for Genomic Studies on Prospective Cohorts*

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ABSTRACT. Objective: The purpose of this study was to develop a quantitative measure of alcohol consumption for gene-mapping studies. **Method:** Using a sample of 3,787 young-adult twin women and an independent sample of 489 men and women from a college drinking study, we developed an alcohol-consumption factor score indexed by (1) maximum typical consumption (log-transformed quantity frequency [LQNTFRQ]), (2) maximum drinks in a 24-hours period (LMAXALC), (3) frequency of drinking five or more drinks per day (FIVE), and (4) frequency of drinking to intoxication (INTOX). We tested (1) for factorial and psychometric equivalence across samples and genders; (2) for construct validity and its equivalence, across samples and genders, using measures of tobacco and cannabis use and family history of alcoholism; and (3) to determine the heritability of the alcohol-consumption factor score using a genetic psychometric model. **Results:** A single-factor model fit well with factor loadings ranging from .60 to .90. With rare

exception, we found support for measurement invariance across the two samples and across genders. Measures of nicotine and cannabis use as well as family history of alcoholism were associated, to a similar extent across samples and genders, with the underlying alcohol-consumption factor. Psychometric twin modeling revealed that each of the alcohol-consumption measures ($h^2 = 34\%-47\%$) and the underlying factor score ($h^2 = 50\%$) were heritable, with the remainder of the variance attributable to individual-specific environmental factors. This moderately heritable alcohol-consumption factor also accounted for a majority of the genetic variance in LQNTFRQ, LMAXALC, FIVE, and INTOX. **Conclusions:** Quantitative measures of alcohol consumption with the favorable attributes of measurement invariance, construct validity, and moderate heritability can greatly enhance future gene-mapping efforts, supplementing information afforded by conventional diagnostic measures of alcohol abuse/dependence. (*J. Stud. Alcohol Drugs* 70: 157-168, 2009)

MEASURES OF SUBSTANCE-USE PROBLEMS as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; American Psychiatric Association, 1994), are becoming more widely applied in genomic studies (e.g., Edenberg et al., 2004; Gelernter et al., 2005, 2006; Luo et al., 2007; Uhl et al., 2001). The popularity of such measures may stem, in part, from the possible clinical implications of discovering genomic regions associated with a psychiatric disorder as defined by established criteria.

A majority of existing genomic studies of alcohol-use disorders, including linkage and genome-wide as well as candidate gene-association studies (Kranzler et al., 1998;

Prescott et al., 2006; Reich, 1996), have used DSM-IV-based diagnostic measures of alcohol abuse and/or dependence as their primary phenotypes. The most notable of these may be the Collaborative Study on the Genetics of Alcoholism (Begleiter et al., 1995), which has had considerable success identifying linkage signals and, consequently, identifying genetic variants in candidate genes, using diagnostic alcohol dependence (Edenberg and Foroud, 2006; Edenberg et al., 2004; Foroud et al., 2000; Reich et al., 1998).

Despite their clinical appeal, diagnostic assessments of alcohol dependence can be particularly problematic in community samples, where the prevalence of meeting criteria for DSM-IV alcohol dependence is relatively low (e.g., in the National Epidemiologic Study of Alcohol and Related Conditions, only 12.5% of the general U.S. population met criteria for DSM-IV alcohol dependence; see Grant, 2000; Saha et al., 2006), thus limiting their utility in genomic studies using community samples. In such cases, quantitative assessments, although reflecting liability to only some aspects of problem drinking (e.g., alcohol consumption), more effectively use data from community samples.

A further challenge of ascertained samples is that the specific constellation of genetic and environmental risk factors that are at play in dense, multiplex families of alcoholics may not extend to the general community. Therefore,

Received: April 14, 2008. Revision: October 6, 2008.

*This research was supported by National Institute on Alcohol Abuse and Alcoholism grants AA09022, HD49024, AA11998, AA07231, AA13987, AA013526, AA017242, and DA019951 and by an Alcoholic Beverage Medical Research Foundation/The Foundation for Alcohol Research grant awarded to Arpana Agrawal.

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community samples represent an informative avenue for the psychometric development of measures of problematic drinking, while allowing for generalization of the etiology of the phenotype to the general population. This is of considerable importance when considering the role of genotype, environment, and their interplay (Heath et al., 1989, 2001).

There are other important concerns surrounding the use of diagnostic, binary measures of alcohol dependence. Using psychometric approaches, several investigators have argued that the diagnostic cutoff of three or more dependence criteria represents an arbitrary truncation of a continuum of alcohol problems and that symptoms of abuse and dependence are, largely, not orthogonal (Bucholz et al., 1996; Cloninger et al., 1988; Hasin et al., 1994; Helzer et al., 2007; Lynskey et al., 2005; Saha et al., 2006, 2007; Schuckit et al., 1995). From a public health perspective, it is also inappropriate to presume that individuals who are heavy alcohol drinkers but endorse fewer than three dependence criteria are problem free. Under the traditional diagnostic model, however, these individuals are considered "unaffected" in linkage and association studies, creating considerable heterogeneity in the pool of unaffected individuals, which may then include low-level drinkers as well as heavy drinkers with one or two symptoms of DSM-IV alcohol dependence.

To optimize the power of detecting linkage and association signals, which is particularly relevant when modeling interactive effects of genotype and environment, the current study attempts to develop a quantitative measure for alcohol consumption—one aspect of alcohol involvement. Such a quantitative factor represents the entire continuum of variation in alcohol consumption found in the general population and, to the extent to which such a continuum is heritable, should also increase our power for gene finding approaches when compared with the standard affected/unaffected categorical approach.

We used four quantitative indices of alcohol consumption: (1) Quantity $\times$ Frequency of alcohol consumption during the 12-month period of heaviest use, (2) a lifetime history of the maximum drinks consumed in a single 24-hour period, (3) frequency of consuming five or more drinks in a day during the 12-month period of heaviest use, and (4) frequency of drinking to intoxication. Using two general population adult midwestern samples, one including same-gender female twins (Missouri Adolescent Female Twin Study [MOAFTS]; Heath et al., 1999) and the other including college-age male and female unrelated subjects ascertained initially through college attendance (College Drinking Study [CDS]; Jackson et al., 2005; Sher, 1991; Sher et al., 1991; Slutske et al., 2004), we investigated:

- (1) evidence for a unidimensional alcohol-consumption factor;
- (2) psychometric equivalence in the factorial structure of alcohol consumption across the MOAFTS and the CDS samples;

- (3) equivalence in the magnitude of the association between correlates of alcohol consumption, such as regular cigarette smoking and cannabis use, and the underlying alcohol-consumption factor across the two studies; and
- (4) the role of heritable influences on the underlying alcohol-consumption factor while accounting for specific genetic influences on each individual index of alcohol consumption in a sample of young-adult female twins.

Method

Samples

We used data from two longitudinal samples from the midwestern United States. The first (MOAFTS) is a sample of female same-gender twin pairs, and the second (CDS) was a sample of unrelated college attending adults, 51% of whom were positive for a family history of alcoholism (Sher, 1991; Traggesser et al., 2007). The longitudinal design of both studies allowed us to ascertain the period of heaviest use based on a self-reported period of maximal alcohol consumption and by assessing over multiple waves of data collection.

Missouri Adolescent Female Twin Study. MOAFTS consists of a cohort of female same-gender twin pairs born between July 1, 1975, and June 30, 1985, who were identified from birth records (Heath et al., 1999; Slutske et al., 2004). Only female twins born to parents who were residents of Missouri were eligible. Twins were eligible to participate if both members of the twin pair had survived past infancy, if both members were not adopted at birth, and if their biological mother was a resident of the state at the time of their birth (as twin pregnancies are considered high risk, inclusion of twin pairs born in-state to out-of-state parents would resample pairs with perinatal complications whose mothers come to the state for medical management of their pregnancy).

Using a cohort-sequential sampling design, twins were invited to participate in the baseline interviews with at least one biological parent, during 1994-1999, when the twins were 13, 15, 17, or 19 years old. Recruitment of 13-year-old twins continued over a 2-year period as twins became age eligible. After obtaining permission from parents, a telephone diagnostic interview was administered to the twins and their parents. Of the 2,369 pairs who were identified as live born, 95.6% were located. The final sample of twins interviewed at baseline for each cohort included 1,633 pairs (72.5% of pairs targeted), including 579, 363, 348, and 343 pairs ages 13, 15, 17, and 19, respectively.

About 13% reported black ethnicity, and 40% of the participants came from rural residences. Further details regarding sample recruitment and characteristics are given elsewhere (Heath et al., 1999; Knopik et al., 2005).

In 2002-2005, twins, irrespective of whether they had participated in any previous interview, were recontacted for interviews if they had not refused recontact or withdrawn

from the study. Wave 4 interview data, including diagnostic assessments of cannabis-use disorders, was obtained from 3,787 female twins, which constitutes MOAFTS Wave 4, the sample that will be used for hypothesis testing. The sample includes 934 monozygotic and 813 dizygotic sister pairs and 293 individual twins whose co-twin did not participate in the study. Of these twins, 3,635 also returned mailed questionnaires. At Wave 4, we were able to complete interviews with both twins from 76% of all pairs of European ancestry identified from birth records and 68% of black twin pairs as well as one twin only from 10% and 12% of pairs of European and black ancestry, respectively.

College Drinking Study. The baseline sample of the CDS comprised 489 freshmen (46% male; mean age = 18.2 years) from a large midwestern university, who were assessed prospectively, using interviews and paper-and-pencil questionnaires, seven times (Years 1, 2, 3, 4, 7, 11, and 16) over a 16-year period. At the original screening, in which 80% of first-time college freshman ($N = 3,156$) participated, criteria from the Short Michigan Alcoholism Screening Test (SMAST; Selzer et al., 1975), adapted to measure paternal and maternal drinking problems (F-SMAST and M-SMAST, respectively; Crews and Sher, 1992), and the Family History-Research Diagnostic Criteria interview (FH-RDC; Spitzer et al., 1978) were used to diagnose paternal family history of alcoholism.

A positive family history was coded if the biological father scored a 4 or more on the F-SMAST (see Sher et al., 1991, for additional details concerning F-SMAST criteria) and met FH-RDC criteria for alcoholism. If no first-degree relative received a diagnosis of alcoholism (FH-RDC criteria), drug abuse, or antisocial personality disorders and there was no alcohol- or drug-use disorder in a second-degree relative, a negative family history was coded.

Selection on these criteria resulted in 808 participants (373 family-history positive and 435 family-history negative), with 601 of these subjects participating in the interviews. Of these, 112 participants were excluded from the final baseline sample ($n = 489$) for a variety of reasons (see Sher et al., 1991, for complete details). Of the 489 subjects in the final baseline sample, 51% could be classified as family-history positive, the remainder being family-history negative. In all, more than 84% of participants were retained over the first 11 years of the study, and more than 78% were retained through Year 16 (mean age = 34.5 years).

Measures

Primary outcome measures. For respondents who reported having consumed more than six alcoholic beverages over their lifetime, four indices of alcohol consumption that were assessed comparably across the two studies were scaled for inclusion in factor analyses. MOAFTS respondents were asked explicitly in Wave 4 to retrospectively report on their

12-month period of heaviest use. In contrast, the 12-month period of heaviest use for the CDS respondents was calculated by using past-12-month data from the questionnaire assessment with the maximum typical consumption. Note that although it is possible to “impute” a zero for each quantitative measure in those who drank six or fewer drinks, this increases skewness in the factor score and can bias estimates of heritability by confounding genetic influences on occasional drinking with those on alcohol consumption. Hence, we opted to exclude those subjects who reported consuming six or fewer drinks over their lifetime.

MAXIMUM TYPICAL CONSUMPTION (LQNTFRQ): Log-transformed quantity frequency variable was created by multiplying the typical frequency at which the respondents drank by the typical quantity they consumed during that same 12-month period and performing a log-transformation to account for skewness. For MOAFTS, respondents were asked on how many days they had any alcoholic drink during their period of heaviest use, with 13 response categories ranging from “1 day/year” to “every day.” For the CDS, nine response categories were offered, ranging from “never” to “1-5 times a year” to “twice a day.” MOAFTS respondents were given 10 categories for typical quantity consumed during the period, ranging from “1-2” to “31 or more.” CDS participants were given nine response options, ranging from “never” to “1 total drink” to “nine or more total.” Based on the response options offered for the two studies, parallel quantity and frequency measures were created (as shown in Table 1).

MAXIMUM DRINKS IN A 24-HOUR PERIOD (LMAXALC): Maximum drinks, which was also log-transformed to account for skewness, was assessed as a lifetime measure and may not have occurred during the respondent’s period of heaviest use. Respondents in both studies were asked to indicate the maximum number of drinks (“in a 24-hour period” in MOAFTS and “in one day” in CDS) without using any list.

FREQUENCY OF HEAVY DRINKING (FIVE): This variable was defined as the frequency at which the respondent drank five or more drinks per day. MOAFTS specified “in a 24-hour period” and referred to the 12-month period of heaviest use; the CDS indicated “at a single sitting” and referred to the past 30 days. A six-level variable was created: “never,” “once a month or less,” “2-3 times per month,” “1-2 times per week,” “3-6 times per week,” and “daily” (see Table 1).

FREQUENCY OF INTOXICATION DURING PERIOD OF HEAVIEST USE (INTOX): This variable was assessed in MOAFTS (for the 12-month period of heaviest use) via a 14-point scale ranging from “never” to “1 day per year” to “every day.” For the CDS, intoxication was assessed for the past 30 days and had eight response categories ranging from “didn’t drink in the past 30 days” to “every day.” As seen in Table 1, INTOX had six levels that were comparable with those of FIVE.

Our choice of these alcohol-consumption indices was driven by the extant literature. Both LQNTFRQ and LMAXALC are part of National Institute on Alcohol Abuse and

TABLE 1. Characteristics of the Missouri Adolescent Female Twin Study (MOAFTS) and the College Drinking Study

Variable	MOAFTS	College Drinking Study	
Demographic characteristics			
Female, %	100.0	52.6	
		Females	Males
Age at assessment, mean (range)	21.7 (18-29)	22.1 (18-36)	22.8 (18-41)
Age at period of heaviest use, mean (range)	19.0 (11-28)	22.1 (18-36)	22.8 (18-41)
Black, % ^a	14.6	4.8	2.9
Family history of alcohol problems, % ^b	36.5	51.6	51.1
Paternal education, % reporting each category			
≤High school	46.4	38.9	40.5
Some college	10.8	5.1	5.6
≥Bachelor's degree	24.1	41.6	34.1
Missing	18.7	14.4	19.8
Maternal education, % reporting each category			
≤High School	45.0	43.6	43.5
Some college	18.1	6.6	6.5
≥Bachelor's degree	22.4	36.6	28.9
Missing	14.6	13.2	21.1
Covariates			
Ever tried cigarettes, %	71.9	75.1	80.6
Regularly smoked, %	34.6	31.1	36.6
	(48.1% of init.)	(41.5% of init.)	(45.5% of init.)
Ever tried cannabis, %	43.0	57.7	66.3
Used cannabis >6 times, %	25.5	35.2	50.5
	(59.3% of init.)	(61.1% of init.)	(76.2% of init.)
Alcohol consumption measures			
Used alcohol >6 times, %	76.8	97.4	98.0
Maximum 24-hour consumption, mean (range) ^c	10.4 (1-86)	9.3 (1-40)	17.3 (1-100)
Typical consumption, heaviest drinking period, % reporting each category ^c			
1-2 drinks	25.6	18.8	10.5
3-4 drinks	32.8	37.2	19.7
5-6 drinks	23.9	28.8	36.0
7-8 drinks	9.9	13.2	19.7
≥9 drinks	7.7	2.0	14.0
Typical frequency, heaviest drinking period, % reporting each category ^c			
1-5 times per year	13.3	4.0	3.5
6-11 times per year	8.3	4.4	1.8
1-3 times per month	26.6	18.4	8.8
1-3 times per week	29.1	44.4	35.5
4-6 times per week	20.6	26.4	44.3
Daily	2.1	2.4	6.1
Frequency of intoxication, heaviest drinking period, % reporting each category ^c			
Never	14.9	38.8	19.7
≤1 time per month	30.8	24.8	24.1
2-3 times per month	24.0	20.0	22.8
1-2 times per week	21.7	13.2	24.1
3-6 times per week	7.8	2.8	7.5
Daily	0.7	0.4	1.8
Frequency of heavy drinking, ≥5 per occasion, % reporting each category, heaviest drinking period ^c			
Never	20.6	40.0	16.8
≤1 time per month	22.7	21.6	10.6
2-3 times per month	21.0	16.0	25.7
1-2 times per week	22.7	18.8	28.3
3-6 times per week	11.8	3.6	15.5
Daily	1.2	0.0	3.1

Notes: Init. = initial. ^aAlmost all nonblack participants were white, as is characteristic of Missouri's population; per Heath et al. (1999) only 26 female twin pairs who were neither white nor black were eligible for the MOAFTS study; 8 College Drinking Study participants were neither white nor black; ^bMOAFTS includes both paternal and maternal history ($n = 206$ maternal only; $n = 940$ paternal only, $n = 235$ both); College Drinking Study includes paternal history only; ^crestricted to participants who had had six or more alcoholic drinks lifetime ($n = 2,903$ MOAFTS; $n = 479$ College Drinking Study).

Alcoholism (NIAAA)—recommended item sets for alcohol consumption (Caetano et al., 1997; Dawson, 1998a,b; Greenfield and Rogers, 1999; Greenfield et al., 2006; Midanik et al., 1996; NIAAA Task Force on Recommended Alcohol Questions, 2003; Room et al., 1995). FIVE as a measure of heavy drinking has been used by investigators to index liability to alcohol dependence (Greenfield et al., 2006; Midanik et al., 2007), and INTOX (American Psychiatric Association, 1994; Kerr et al., 2006; Knupfer, 1984) is a clinically recognized alcohol-induced disorder.

Covariates. Four substance-related covariates were created to examine external construct validity.

FAMILY HISTORY OF ALCOHOL PROBLEMS: This variable was coded using family-history positive or negative in CDS and using twin reports that either mother or father (queried separately for each parent) “had problems with police, work, family” or “thought mom/dad was an excessive drinker.”

REGULAR CIGARETTE SMOKING: Smoking was assessed via self-reported lifetime history of smoking 100 or more cigarettes.

CANNABIS USE: This item was assessed by self-reported lifetime history of ever using cannabis.

CANNABIS USE SIX OR MORE TIMES: The fourth substance-related covariate was self-reported lifetime history of having used cannabis six or more times.

Final sample sizes

Of the 3,787 women who participated in the MOAFTS Wave 4 assessment, 2,903 participants had consumed at least six alcoholic beverages, and, of these, 2,831 had data for all four alcohol-consumption measures and were included in the present analyses. Sample selection for the CDS was based on the period of heaviest use (as indexed by the 12-month period with the highest reported frequency of drinking multiplied by quantity consumed). Using this strategy, data from Wave 1 were used for 20.7% of respondents, with data from 18.6%, 16.2%, 15.8%, 11.7%, 6.5%, and 10.6% of respondents coming from Waves 2-7, respectively. Of the 479 participants in the CDS who had consumed at least six alcoholic beverages, 459 had complete data for all four alcohol-consumption measures and were included in the present analyses.

Table 1 presents the endorsement rates for the MOAFTS and the CDS. As might be expected given that the MOAFTS sample is population based and the CDS sample is college students, there are differences in demographic and substance-use characteristics across the samples. The prevalence of abstinence from alcohol is considerably lower in CDS, but this is reflective of primarily residential midwestern U.S. colleges with large fraternity/sorority systems and a focus on inter-collegiate sports. Comparable estimates of abstinence were found in the National Epidemiological Study of Alcoholism and Related Conditions (NESARC) when subsetting on some

of these characteristics (Dawson et al., 2005, 2008; Grant et al., 2003).

Phenotypic statistical analyses

Factor structure of alcohol consumption. Exploratory factor analyses were conducted separately for MOAFTS and for the men and women from the CDS in SAS (Version 8.2; SAS Institute, Inc., Cary, NC). Selection of the appropriate number of factors was done by examination of eigenvalues, factor loadings, and visual inspection of the scree plot.

Test of factorial invariance. After confirming the presence of unidimensionality (i.e., whether a single factor explained the covariance between the alcohol-consumption measures), confirmatory factor models were fit in MPlus (Version 4.1; Muthén and Muthén, 2004) using three groups: MOAFTS, CDS (men), and CDS (women) (Muthén and Asparouhav, 2002). In the baseline model, mean and variance of the underlying factor score were constrained to 0 and 1, respectively, across all three groups. In this baseline model, intercepts (similar to means but for continuous dependent measures) were allowed to vary across the three groups, but factor loadings were constrained across the three groups. Therefore, the baseline model allowed for mean differences in the alcohol-consumption measures (LQNTFRQ, LMAXALC, FIVE, INTOX) while forcing invariance in factor loadings.

An omnibus test of factorial noninvariance (i.e., whether all four factor loadings were different across all three groups) was not identified, and hence, we systematically allowed the factor loading of each alcohol-consumption measure to be freely estimated across MOAFTS, CDS (men), and CDS (women). When this model suggested an improvement in fit, constraints were placed, first by gender (i.e., whether factor loadings could be equated across MOAFTS [women] and CDS [women] but free in CDS [men]) and then by sample (i.e., whether factor loadings could be equated across CDS [women] and CDS [men] but free in MOAFTS). The best-fitting model was selected based on change in chi-square model fit.

Effects of substance-related covariates on the factor score. To examine whether measures of family history of alcoholism, cigarette smoking, and cannabis use were associated with the underlying alcohol-consumption factor, the regression of the latent alcohol-consumption factor on each covariate was included in the model (MacIntosh and Hashim, 2003). We also tested whether the association between family history of alcoholism, cigarette smoking, and cannabis use and the latent factor could be equated across the three groups.

Twin analyses

To compute the extent to which heritable factors contributed to variance in the alcohol-consumption factor score, we used data from MOAFTS, which included 3,787

FIGURE 1. Best-fitting genetically informative psychometric model of alcohol consumption in the Missouri Adolescent Female Twin Study. LQNTFRQ = log-transformed quantity frequency; LMAXALC = maximum drinks in a 24-hour period; FIVE = frequency of drinking five or more drinks per day; INTOX = frequency of drinking to intoxication.

twin women, 2,831 of whom had no missing data on the four alcohol-consumption indices (644 monozygotic pairs, 500 dizygotic pairs, and one member from 541 pairs; one pair of unknown zygosity was deleted from these analyses). A multivariate psychometric (or common pathway) model (Kendler et al., 1987), which may be considered a genetically informative equivalent of the phenotypic factor analyses, was fitted to the data with variance in each of the alcohol-consumption measures and in the underlying factor explained by additive genetic (A), shared environmental (C), and individual-specific environmental (E) influences. Monozygotic and dizygotic twins share 100% and 50% of their genes (identical-by-descent), respectively, and, under the equal-environments assumption, both zygosity types share 100% of their shared environment. Estimates of E include measurement error and, by definition, are uncorrelated across members of twin pairs.

The best-fitting psychometric/common pathway model is presented in Figure 1—it assumes, much like the phenotypic factor model, that underlying the four alcohol-consumption measures (LQNTFRQ, LMAXALC, FIVE, and INTOX) is

a unidimensional alcohol-consumption factor score. There are also two sources of genetic and environmental influence in the model—those that specifically influence each alcohol-consumption measure (As and Es in Figure 1) and those that indirectly influence the alcohol-consumption measures via their factor loadings on the underlying factor score (Ac and Ec in Figure 1). For example, variance in LQNTFRQ is attributed to As and Es (Cs not shown in Figure 1) and also by the product of Ac and Ec with the corresponding factor loading. Therefore, this model (1) allows us to estimate the heritability of each alcohol-consumption measure as well as the underlying alcohol-consumption factor score and (2) decomposes these variance components into their common and specific sources.

All twin modeling was conducted in the statistical software package Mx (Neale et al., 2004), using raw data and the full information maximum likelihood estimator. The statistical significance of parameters was tested by comparing the difference in the -2 log likelihood fit of the full model and respective submodels—this difference follows a chi-square distribution for given degrees of freedom.

TABLE 2. Standardized factor loadings in Missouri Adolescent Female Twin Study (MOAFTS) and the College Drinking Study samples for the confirmatory factor analysis on an alcohol consumption factor score using log-transformed quantity frequency (LQNTFRQ), maximum drinks in a 24-hour period (LMAXALC), frequency of drinking five or more drinks per day (FIVE), and frequency of drinking to intoxication (INTOX)

Variable	MOAFTS (<i>n</i> = 2,831)	College Drinking Study	
		Women (<i>n</i> = 242)	Men (<i>n</i> = 217)
LQNTFRQ	.87	.60	.81
LMAXALC	.61	.48	.61
FIVE	.90	.86	.71
INTOX	.83	.68	.66
Total variance	.99	.34	.73
Variance explained by factor	61%	43%	48%

Note: Variance explained by each factor is computed by summing the square of each factor loading to obtain the eigenvalue and then dividing the eigenvalue by the number of items (i.e., 4).

Results

Phenotypic analyses

Factor structure of alcohol consumption. A single-factor model fit our data well, with eigenvalues for the first factor being 2.57, 1.78, and 1.96 for MOAFTS, CDS (men), and CDS (women), respectively. The second eigenvalue was uniformly low (0.1–0.3), and this was confirmed by visual inspection of the scree plots. Factor loadings for the unidimensional model are presented in Table 2. Overall, the factor structure for alcohol consumption as indexed by four quantitative alcohol-consumption measures (LQNTFRQ, LMAXALC, FIVE, and INTOX) was consistent across samples and across genders, although factor loadings were somewhat lower in the CDS.

Test of factorial invariance. The baseline model—where intercepts were free and factor loadings and factor means

(equated to 0) and variances (equated to 1.0) were constrained to be equal across MOAFTS, CDS (men), and CDS (women)—provided acceptable fit to our data (comparative fit index [CFI] = .94, Tucker-Lewis index [TLI] = .91, standardized root mean squared residual [SRMR] = .12) (Bollen and Long, 1993). Model misfit was partly attributable to the uneven sample sizes—for instance, in MOAFTS, CFI and TLI were greater than .96, and SRMR was .03, indicating good fit. Models that allowed for the factor loadings of LMAXALC and INTOX to be free across the three groups did not improve model fit (LMAXALC: $\Delta\chi^2 = 3.8$, 2 df; and INTOX: $\Delta\chi^2 = 2.8$, 2 df). However, for LQNTFRQ, factor loadings were free across samples but could be constrained across genders in the CDS ($\Delta\chi^2 = 10.5$, 1 df), whereas for FIVE, factor loadings could not be constrained across any of the three groups without a considerable deterioration in fit ($\Delta\chi^2 = 29.6$, 2 df).

Effects of substance-related covariates on the factor score.

In all three groups, a family history of alcohol problems (b [SE] = 0.08 [0.04]), regular cigarette smoking (b = 0.55 [0.04]), lifetime cannabis use (b = 0.37 [0.05]), and cannabis use six or more times (b = 0.33 [0.05]) were significantly associated with the underlying alcohol-consumption factor score. The strength of these regression coefficients did not vary across the three ($\Delta\chi^2 = 11.76$, 8 df).

Twin analyses

Table 3 shows the within- and across-twin correlations between the four alcohol-consumption measures and the factor score. Within-person correlations between the individual measures and between each measure and the factor score were high. From the genetic perspective, correlations within and across phenotypes between members of a twin pair are particularly informative. As shown in Table 3, across-twin

TABLE 3. Within- and across-twin correlations between the four alcohol-consumption measures (log-transformed quantity frequency [LQNTFRQ], maximum drinks in a 24-hour period [LMAXALC], frequency of drinking five or more drinks per day [FIVE], and frequency of drinking to intoxication [INTOX]) and the alcohol-consumption factor score in 644 monozygotic and 500 dizygotic female twin pairs from the Missouri Adolescent Female Twin Study

Variable	TWIN 1					TWIN 2				
	LQNTFRQ	LMAXALC	FIVE	INTOX	FACTOR	LQNTFRQ	LMAXALC	FIVE	INTOX	FACTOR
Twin 1										
LQNTFRQ	1.00	.59	.78	.70	.93	.33	.27	.26	.21	.31
LMAXALC	.63	1.00	.53	.45	.66	.25	.23	.21	.18	.25
FIVE	.78	.52	1.00	.78	.94	.24	.20	.21	.20	.25
INTOX	.68	.44	.79	1.00	.86	.23	.18	.21	.19	.24
FACTOR	.92	.67	.94	.85	1.00	.31	.25	.25	.22	.30
Twin 2										
LQNTFRQ	.47	.39	.40	.37	.47	1.00	.63	.78	.71	.93
LMAXALC	.44	.50	.39	.34	.46	.63	1.00	.50	.41	.65
FIVE	.33	.31	.30	.33	.36	.70	.51	1.00	.82	.94
INTOX	.31	.26	.29	.30	.33	.77	.45	.77	1.00	.88
FACTOR	.44	.39	.39	.38	.45	.93	.66	.93	.86	1.00

Notes: Monozygotic correlations are below the diagonal and dizygotic correlations are above the diagonal. The within-person across-phenotype correlations (e.g., Twin 1's LMAXALC with Twin 1's FIVE) are unshaded. The across-twin correlations (i.e., between Twin 1 and Twin 2) are shaded; the across-twin within-phenotype correlations (e.g., Twin 1's LMAXALC with Twin 2's LMAXALC) are **bolded** within the gray boxes.

TABLE 4. The influence of additive genetic (heritability, A_c and A_s from Figure 1) and individual-specific environmental factors (E_c and E_s from Figure 1) of four measures assessing alcohol consumption and on the underlying alcohol factor score in 2,831 the Missouri Adolescent Female Twin Study female twins; all numbers are standardized to a variance of 1.0 (i.e., .76 is 76% of a total 100% variance)

Variable	LQNTFRQ			LMAXALC			FIVE			INTOX			Alcohol factor score
	Total	Common	Specific	Total	Common	Specific	Total	Common	Specific	Total	Common	Specific	
Variance	1.0	.76	.24	1.0	.38	.62	1.0	.82	.18	1.0	.68	.32	1.00
Heritability	.47	.83	.17	.37	.51	.49	.41	1.0	0.0	.34	1.0	0.0	.50
Individual-specific environment	.53	.70	.30	.63	.30	.70	.59	.69	.31	.66	.52	.48	.50
Standardized factor loading		.87			.60			.90			.83		

Notes: Common and specific variances are calculated from total variance; common and specific heritabilities are calculated from total heritability (and not from total variance)—that is, for log-transformed quantity frequency (LQNTFRQ), 76% of the total variance (1.0) is common; 83% of the total heritability (which makes up 47% of the total variance) is common. To calculate proportion of total variance that is attributable to common heritable factors, multiply .47 (% of variance attributable to heritable factors) by .83 (% of variance attributable to common heritable factors), which is .39. LMAXALC = maximum drinks in a 24-hour period; FIVE = frequency of drinking five or more drinks per day; INTOX = frequency of drinking to intoxication.

correlations in monozygotic twin pairs consistently exceeded those in dizygotic pairs, highlighting the role of genetic influences. Dizygotic across-twin correlations for all measures except LMAXALC were greater than half the corresponding monozygotic correlations, suggesting the possible role of shared environmental influences.

Results from the multivariate common-factor model are presented in Table 4 and Figure 1. Despite the dizygotic correlations being greater than half the monozygotic correlations, both common and specific shared environmental influences could be constrained to zero ($\Delta\chi^2 = 5.42$, 5 df, $p = .37$) in the twin model. The common genetic (A_c) and individual-specific (E_c) factors each explained 50% of the total variance in the underlying alcohol-consumption factor score. Overall, each of the four alcohol-consumption indices were also moderately heritable (34%–47%; see Table 4). Factor loadings from this underlying factor score to each quantitative index of alcohol consumption were high (.60–.90; see Table 4). There was evidence for smaller specific genetic (A_s) influences on LQNTFRQ and on LMAXALC but not on FIVE and INTOX. About 76% of the variance in LQNTFRQ was shared with the underlying alcohol-consumption factor, whereas the remaining variance was attributable to A_s and E_s (Table 4). For LMAXALC, 38% of the variance was shared, whereas the remainder was attributable to A_s and E_s . This latter finding is consistent with the somewhat lower factor loading for LMAXALC in the phenotypic factor analyses. For both FIVE and INTOX, all genetic variances were attributable to A_c , with specific variance being attributable to E_s (31% and 48%, respectively).

Discussion

Using two midwestern U.S. samples, we sought to examine the factor structure and heritability of a quantitative alcohol-consumption factor, which we propose as a phenotype with great promise for genomic studies of alcohol-re-

lated behavior. The four alcohol-consumption measures of LQNTFRQ, LMAXALC, FIVE, and INTOX loaded well on the underlying factor in both samples, with evidence in favor of factorial invariance across them. This underlying alcohol-consumption factor was moderately heritable (50%) and captured a majority of genetic variance in each individual consumption measure.

The heritability of the alcohol-consumption factor score is approximately equal to published estimates of heritable influences on DSM-IV-based measures of alcohol dependence (Heath et al., 1997; McGue et al., 2000; Prescott and Kendler, 1995, 1999; Rhee et al., 2006; True et al., 1999). Using the precalculated alcohol-consumption factor score, we found a highly comparable heritability of 47% in our sample (full model: $a^2 = .31$ [95% confidence interval [C.I.]: .12–.50]; $c^2 = .16$, [95% C.I.: .00–.32], $e^2 = .53$ [95% C.I.: .48–.59], but c^2 could be constrained to 0, yielding $a^2 = .47$; results available on request). However, heritability studies of each of the individual alcohol-consumption measures are fewer. Saccone and colleagues (2000) previously reported a familial correlation of 0.41–0.46 for LMAXALC. Recently, using several large twin datasets available from the Australian Twin Registry, Hansell and colleagues (2008) demonstrated a heritability of .31 and .51 for LQNTFRQ in younger and older Australian adult twins, respectively. Several additional studies have estimated that heritable influences on the frequency component of LQNTFRQ range from 37% to 42% (Pagan et al., 2006; Poelen et al., 2008; Viken et al., 1999), whereas Slutske et al. (1999) reported similar estimates for a set of related alcohol-consumption measures. Fowler et al. (2007) reported a heritability of .64 for quantity of alcohol consumption.

Quantitative trait measures of noncategorical phenotypes or behaviors can yield considerable increases in power for the detection of linkage and association signals. Some prior studies have used quantitative indices of alcohol consumption for linkage. For instance, Kuo et al. (2006) used quantitative

indices of tolerance, a factor score of withdrawal symptoms, and the maximum drinks measure (i.e., LMAXALC) for linkage analyses that identified elevations on chromosomes 6, 2, 12, 15, and 18. Other studies (Agrawal et al., 2008; Bergen et al., 2003; Prescott et al., 2006; Saccone et al., 2000) have used a symptom count of alcohol-dependence (DSM-Third Edition, Revised [DSM-III-R; American Psychiatric Association, 1987] or DSM-IV) symptoms or LMAXALC alone as quantitative measures of risk of alcoholism, particularly to identify several regions on chromosome 4 as areas of putative genomic interest. Our measure of alcohol consumption, which is moderately heritable, has three unique advantages over these existing measures.

First, unlike diagnostic items, measures of consumption also encompass a wide range of behavior responses. Second, as a composite measure across four consumption items, it pools genetic variance across these informative indices of alcohol use, unlike other studies, which have used the individual indices themselves. Third, it is not limited in range as is an alcohol-dependence symptom count (must range from 0 to 9 for DSM-III-R or 0 to 7 for DSM-IV, whereas a factor score is continuously distributed and can take on any value, e.g., from -3.0 to +3.0) and is free from the psychometric variations across versions of the alcohol dependence assessment (DSM-III-R vs DSM-IV).

It is noteworthy that the alcohol-consumption factor score was robust, with only modest differences in factor loadings across samples or genders and a uniformly significant external validity as indexed by associations with aspects of family history, cigarette smoking, and cannabis involvement. This is particularly relevant given the differences between the samples used for analysis: The MOAFTS sample was ascertained using a cohort-sequential design from birth records, and responses for the period of heaviest use were determined from the fourth wave of data collection via telephone interview, whereas the CDS ascertained male and female college drinkers based on a family history of alcoholism and used questionnaires for data collection, and period of heaviest use was determined from the prior 12 months. Despite these variations in ascertainment strategy, sample characteristics, and the construction of each alcohol-consumption item (see the Method section), we converged on a highly comparable factor solution. The internal and external validity of the factor score suggests that similarly cohesive and valid alcohol-consumption measures can be devised in other independent studies even if they have differing sampling schemes and use different but comparable instruments. Our own preliminary work has also shown that inclusion of additional consumption measures (or exclusion of one measure, owing to unavailability) does not severely modify the factor structure—this allows flexible extensions of the alcohol-consumption factor score. This level of robustness is essential for future gene-mapping efforts to facilitate

the process of replication (Cardon and Bell, 2001; Chanock et al., 2007).

The factor score represents an important aspect of liability to problematic drinking—that associated with consumption. It is potentially an index of tolerance and drinking in larger quantities or for longer than intended (American Psychiatric Association, 1994). However, other domains of problematic drinking and alcoholism, such as physiological and psychological sequelae and disruption of social and occupational functioning, may not be effectively captured by the alcohol-consumption factor score. It is likely that such quantitative indices exist for other dimensions of problematic drinking (e.g., withdrawal). Developing such measures will allow investigators to test the extent to which genetic influences on our alcohol-consumption factor score overlap other aspects of problem drinking.

Some important limitations of our study need to be considered. First, we did not have access to a sample of adult male twins, and, consequently, we are not aware of whether similar heritability estimates would be captured in a sample of young adult men. Second, both of our samples were collected in midwestern states, and our findings may not extrapolate to other regions. It is also important to note that some of the younger participants may not have been past their period of risk for heavy drinking, and, hence, examining future waves of data may be necessary. Third, to allow for comparability with MOAFTS, CDS data on all measures were extracted from the wave at which the participant reported the highest LQNTFRQ—this may not have coincided with the year in which the participant had highest reports on other measures. Fourth, it is important to consider that any genomic studies conducted with the factor score will aim to identify genetic influences common to the four measures of alcohol consumption but may not successfully target measure-specific genes. Particularly for LMAXALC, which was influenced by specific genetic factors, investigators may wish to consider testing for measure-specific genetic and genomic influences. Fifth, our measures are reliant on the accuracy of retrospective reporting. Finally, we may have been restricted by sample sizes, and, consequently, our ability to constrain a majority of the factor loadings across the larger MOAFTS and smaller CDS samples and to drop shared environmental influences from our twin models may be reflective of reduced power.

Notwithstanding these limitations, using four quantitative alcohol-consumption measures, we developed a quantitative phenotype that generalizes to multiple samples with minimal measurement distortion, has reasonable construct validity, and is moderately heritable. Although this is a first and important step toward creating a powerful and flexible phenotype for future gene-mapping efforts, replication of the factor structure and its invariance across independent samples using varied assessment instruments is required. With adequate replication and refinement, eventually a set

of scoring coefficients may allow investigators to scale their alcohol-consumption data to a common metric allowing comparability across several independent genomic and Gene $\times$ Environment analyses.

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