Genetic Influences on Alcohol-related Hangover

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Abstract

Aims. To quantify the relative contributions of genetic and environmental factors to alcohol hangover. **Design.** Biometric models were used to partition the variance in hangover phenotypes. **Setting.** A community-based sample of Australian twins. **Participants.** Members of the Australian Twin Registry, Cohort II who reported consuming alcohol in the past year when surveyed in 2004-2007 (N= 4,496). **Measurements.** Telephone interviews assessed participants' frequency of drinking to intoxication and frequency of hangover the day after drinking. Analyses examined three phenotypes: *hangover frequency*, *hangover susceptibility* (i.e., residual variance in hangover frequency after accounting for intoxication frequency) and *hangover resistance* (a dichotomous variable defined as having been intoxicated at least once in the past year with no reported hangovers). **Findings.** Genetic factors accounted for 45% (95% confidence interval [CI] = 37-53%) and 40% (95% CI = 33-48%) of the variation in hangover frequency in men and women, respectively. Most of the genetic variation in hangover frequency overlapped with genetic contributions to intoxication frequency. Genetic influences accounted for 24% (95% CI = 14-35%) and 16% (95% CI 8-25%) of the residual hangover susceptibility variance in men and women, respectively. Forty-three percent (95% CI 22-63%) of the variation in hangover resistance was explained by genetic influences, with no evidence for significant sex differences. There was no evidence for shared environmental influences for any of the hangover phenotypes. **Conclusions.** Individual differences in the propensity to experience a hangover and of being resistant to hangover at a given level of alcohol use are genetically influenced.

Genetic Influences on Alcohol-related Hangover

Alcohol hangover – a constellation of unpleasant symptoms that emerge as the blood alcohol concentration approaches zero after excessive alcohol use – is one of the most common adverse consequences of drinking [1-3]. Hangover measures are cross-sectionally and prospectively associated with problematic drinking [4-7]. Frequent hangover has been associated with depression symptoms [8] and increased risk for several causes of mortality in adults [9, 10]. In young people, frequent hangover has been associated with decreased white matter integrity in the frontal lobe and cerebellum [11] and impairments in sustained attention [12]. These associations might arise because hangover reports are sensitive markers of very heavy episodic alcohol exposures [5, 13] or serve as proxies for important behavioral risk processes (e.g., inability to learn from punishment, impaired control over drinking). Additionally, the pathophysiology of hangover involves inflammatory responses that may contribute directly to some adverse neurocognitive and health outcomes [14].

A high dose of alcohol is a prerequisite for experiencing a hangover, but there are substantial individual differences in hangover responses even when alcohol exposure is experimentally controlled [15]. Several lines of evidence indicate that this variation in hangover susceptibility is at least partly accounted for by genetic factors. Most notably, *ADH1B* and *ALDH2* genotypes associated with a flushing response to alcohol consumption have been related to heightened hangover susceptibility [16-18]. Several studies have demonstrated excess hangover in drinkers with a family history of alcoholism [4, 7, 19, 20], though null findings have also been reported [21-23]. Finally, hangovers have been related to the level of subjective response to alcohol [6, 24, 25], a prominent endophenotype in alcoholism research [26-28].

Variations in the assessment of the hangover phenotype may require different theoretical interpretations and have distinct correlates. In particular, it is important to distinguish between measures tapping hangover *vulnerability* and *frequency* [5]. *Vulnerability* measures tap individual differences in pharmacologic response to alcohol effects. Hangover frequency is a more complex phenotype that is likely to be related to vulnerability, but may also reflect a broader set of determinants, such as individual differences in drinking patterns, impulsivity or loss of control over drinking, and ability to learn from punishment. An important motivation to distinguish between these two hangover phenotypes is the mounting evidence suggesting that frequent hangover is associated with *lower* subjective responses to alcohol and *increased* risk for alcohol use disorder, whereas hangover vulnerability is associated with *higher* subjective responses to alcohol and *decreased* risk for alcohol use disorder [4, 6, 24].

In the current research, we examined three hangover phenotypes: the frequency of past-year hangover and two indicators of hangover vulnerability (hangover susceptibility and hangover resistance). Although existing evidence strongly suggests a genetic contribution to hangover, there has been no research to quantify the relative contributions of genetic and environmental factors to hangover reports. The current study extends the literature by addressing this question using data collected from a large, community-recruited twin sample. Based on prior research, we expected that genetic factors would explain a substantial proportion of variance in each hangover phenotype and that a portion of the genetic variation in hangover frequency would overlap with genetic contributions to alcohol consumption patterns.

Methods

Participants

Participants for this study were 4,764 members of the Australian Twin Registry (ATR) Cohort II (for more details about the study participants and the zygosity determination, see [29]). In 2004-2007, a telephone interview containing an assessment of alcohol use including questions about hangover was conducted with the ATR Cohort II members (individual response rate of 80.4%). The mean age was 37.7 years (range = 32-43) and 57.2% of the sample was female. The focus of this investigation was the 4,496 (94%) participants that had consumed alcohol in the past year. This included 1,693 complete twin pairs and 1,110 individual twins from incomplete pairs. The ancestry of the majority of these participants was Northern European (66%), with sizable fractions also of Southern European (8%), Western European (8%), and (any) Asian ancestry (1.3%).

Procedure

Twins were assessed by structured telephone interview. Interviews were administered by trained lay-interviewers who were blind to the status of the cotwin. All interviews were tape-recorded and a random sample of 5% of the interview tapes was reviewed for quality control and coding inconsistencies. A small sub-sample of the participants were re-interviewed within six months after their initial interview to establish the test-retest reliability of the interview measures (N = 154, mean retest interval = 3.2 months, SD = 1.2 months, range = $1.2 - 6.0$ months). This study was approved by the Institutional Review Boards at the University of Missouri and the Queensland Institute of Medical Research. All of the participants provided informed consent.

Measures

Intoxication frequency was assessed by asking participants on how many days in the past year they got drunk as indicated by slurred speech or unsteadiness (test-retest $r = 0.87$). Three measures of past-year alcohol-related hangover were examined. *Hangover frequency* (test-retest $r = .82$) was assessed by asking participants on how many days in the past year they did not feel well the day after drinking. Two approaches to examining hangover vulnerability were taken. One approach, employed in prior survey investigations, was to use the residual variance in hangover frequency after accounting for the frequency of drinking to intoxication as an index of *hangover susceptibility* [4, 7, 19, 21]. Another approach was to identify individuals that were especially low in hangover susceptibility, that is, they were hangover resistant (aka hangover "insensitive" or "immune"). *Hangover resistance* (test-retest $r = .72$) was a dichotomous variable defined as getting drunk at least once in the past year without experiencing a hangover, compared to getting drunk at least once in the past year and experiencing at least one hangover. This approach is analogous to that used by Howland and colleagues in their review of the prevalence of hangover resistance [15]. In the current study, hangover resistance was defined only for the 2,619 participants (58% of past-year non-abstainers) who had been intoxicated in the past year.

Data Analysis

The measures of the past-year frequencies of hangover and intoxication were log-transformed and standardized prior to analysis to reduce the skewness and kurtosis of their distributions. All analyses were conducted using the Mplus program (Version 6.1) [30]. Biometric models were fitted directly to the raw twin data, using data from incomplete as well as complete twin pairs, by the method of full information maximum likelihood for the analysis of the continuous hangover frequency phenotype, and robust weighted least squares for the analysis

of the categorical hangover resistance phenotype. Univariate biometric model-fitting was conducted to partition the variation in each hangover index, considered individually, into additive genetic (A), shared environmental (C) or nonadditive genetic (D), and unique environmental influences (E). Because C and D cannot be simultaneously estimated when using only twin data, a decision had to be made about whether to include C or D. For both hangover frequency and resistance, an ADE model provided a better fit to the data than an ACE model. One set of models allowed different parameter estimates for men and women. Another set of models constrained the parameter estimates for men and women to be equal. Evidence for quantitative sex differences was evaluated by comparing the fits of models that equated the parameter estimates in men and women to models that allowed the parameter estimates for men and women to differ. Evidence for qualitative sex differences was evaluated by comparing the fits of the models that fixed the genetic correlation between men and women to unity to a model in which the genetic correlation was freely estimated at a value less than one. This is based on comparing the magnitude of the opposite-sex dizygotic to the same-sex dizygotic twin correlations.

A different approach was used to partition the variation in hangover susceptibility. A bivariate biometric model was fitted to examine the proportion of genetic variation in hangover frequency that could be explained by genes influencing individual differences in the frequency of alcohol intoxication, and also to examine the causes of variation in the residual component, a putative index of hangover susceptibility. A Cholesky decomposition [33] was implemented to partition the genetic and environmental influences on alcohol hangover into portions that were shared with the frequency of intoxication, and residual portions that were not shared with alcohol intoxication (see Figure 1).

[insert Figure 1 about here]

Results

Level of alcohol involvement among participants

On average, participants had consumed alcohol on 111 days (about twice a week) and been intoxicated on 10 days (about once a month) in the past year. The typical quantity of alcohol consumed on a drinking occasion in the past year was about 3 drinks. Men drank significantly more than women. On average, participants suffered from 6.24 alcohol-related hangovers in the past year (men: 8.53, women: 4.51). Among those participants who had been drunk at least once in the past year, 14.72% (men: 14.17%, women: 15.33%) were classified as hangover resistant.

Twin correlations

Inspection of twin correlations provided preliminary information about the contribution of genetic and environmental influences to individual differences in hangover (see Table 1). For example, the MZ twin correlations were larger than the DZ twin correlations among both men and women for hangover frequency, suggesting that genetic factors were important in explaining individual differences in both sexes.

Univariate biometric model-fitting

More rigorous tests of the contributions of genetic and environmental influences to individual differences in hangover were obtained from univariate biometric model fitting of the twin data for hangover frequency and resistance (see Table 2). (The contributions of genetic and environmental influences to individual differences in hangover susceptibility were estimated within a bivariate model.) In the full model that included additive genetic, non-additive genetic, and unique environmental contributions to variation in hangover frequency, the estimates of non-

additive genetic effects were not significantly greater than zero. A reduced model that dropped

non-additive genetic influences did not significantly worsen model fit ($\Delta\chi^2 = 0.26$, df = 2, p =

.88). There was evidence for quantitative sex differences, that is, there was a significant

deterioration in model fit ($\Delta\chi^2 = 57.68$, $df = 2$, $p < .0001$) when the parameter estimates of the

proportion of variation in hangover frequency explained by genetic and environmental influences

were equated for men and women. In the model that allowed the parameter estimates for men

and women to differ, genetic and unique environmental factors explained 45% and 55% of the

variation in hangover frequency in men, and 40% and 60% of the variation in hangover

frequency in women. There was also evidence for qualitative sex differences in this model, that

is, there was a significant deterioration in model fit when the genetic influences contributing to

variation among men and women were perfectly correlated ($\Delta\chi2 = 6.65$, df = 1, p = .01). The

correlation between the latent genetic factor in men and women was 0.42 (95% confidence

interval [CI] .00, .86).

In a full model that included additive genetic, non-additive genetic, and unique

environmental contributions to variation in hangover resistance, the estimates of additive and

non-additive genetic effects were not significantly greater than zero (see Table 2). A reduced

model that dropped non-additive genetic influences did not significantly worsen model fit ($\Delta\chi^2 =$

1.72, df = 2, p = .42) and resulted in significant genetic effects. There was no evidence for

quantitative sex differences, that is, there was not a significant deterioration in model fit when

the proportion of variation in the liability to be hangover resistant explained by genetic and

environmental influences were equated for men and women ($\Delta\chi^2 = 0.18$, df = 1, p = .67). In the

model that equated parameter estimates for men and women, genetic and unique environmental

factors explained 43% and 57% of the variation in hangover resistance. There was no evidence

for qualitative sex differences in this model, that is, there was not a significant deterioration in model fit when the genetic influences contributing to variation among men and women were perfectly correlated ($\Delta\chi^2 = 0.41$, df = 1, p = .52).

Bivariate biometric model-fitting of hangover susceptibility

The frequency of drinking to intoxication and hangover frequency were highly correlated $r = .78$ ($r = .74$ among men, $r = .79$ among women). Inspection of the cross-trait twin correlations provided preliminary information about the role of genetic and environmental factors in explaining this association (see Table 1). The cross-trait twin correlations between frequency of intoxication and hangover frequency were nearly as large as the within-trait twin correlations for hangover frequency. For example, the cross-trait correlation between frequency of intoxication and hangover frequency and the within-trait correlation for hangover frequency among MZ males were 0.43 and 0.44, respectively. This suggests that there is a large overlap in the familial contributions to the frequency of drinking to intoxication and frequency of experiencing hangover.

A bivariate biometric model was fitted to the twin data to decompose the variation in hangover frequency into genetic and environmental sources shared and not shared with alcohol intoxication. We focused on estimates from a model that allowed for sex-specific parameter estimates because a model that equated the parameter estimates for men and women provided a significantly worse fit to the data ($\Delta\chi^2 = 229.36$, $df = 6$, $p < .0001$). Following from the univariate results, a reduced bivariate AE model (depicted in Figure 1) rather than an ADE model was employed.

Most, but not all, of the genetic and environmental variation in hangover frequency was explained by genetic and environmental variation in common with intoxication frequency (see

Table 3). For instance, genetic influences related to intoxication explained 75% (95% CI = 65-85%) and 86% (95% CI = 78-93%) of the genetic variation in hangover frequency in men and women, respectively. Of the remaining variation (hangover susceptibility), genetic and unique environmental factors explained 24% (95% CI = 14-35%) and 76% (95% CI = 65-86%) of the variation among men, and 16% (95% CI = 8-25%) and 84% (95% CI = 75-92%) of the variation among women. There was no evidence for qualitative sex differences in the genetic influences contributing to hangover susceptibility in this model ($\Delta\chi^2 = 1.72$, $df = 1$, $p = .19$).

Bivariate biometric model-fitting of hangover resistance

Individuals classified as hangover resistant differed from those classified as non-resistant in their levels of alcohol consumption. Hangover resistant individuals reported that they had been intoxicated fewer times in the past year than hangover non-resistant individuals (on 11.22 versus 17.17 days; $t = 8.65$, $p < .0001$). Therefore, an approach similar to that used with hangover susceptibility was employed to remove the portions of genetic and environmental variation in hangover resistance that were potentially explained by individual differences in the frequency of drinking to intoxication. Again, we focused on estimates from a model that allowed for sex-specific parameter estimates because a model that equated the parameter estimates for men and women provided a significantly worse fit to the data (owing to differences in the estimates for intoxication frequency). In contrast to the results for hangover frequency, genetic and environmental influences contributing to variation in the frequency of intoxication did not explain significant portions of the genetic and environmental influences on hangover resistance (see Table 4). Genetic influences related to intoxication explained only 18% (95% CI = 0-41%) and 16% (95% CI = 0-40%) of the genetic variation in hangover resistance in men and women, respectively. Of the remaining variation in hangover resistance, genetic and unique

environmental factors explained 34% (95% CI = 4-64%) and 66% (95% CI = 36-96%) of the

variation among men, and 41% (95% CI = 9-72%) and 59% (95% CI = 28-91%) of the variation

among women.

Discussion

We investigated the biometric structure of alcohol-related hangover using data from a community-based sample of Australian twins. The findings consistently implicated latent genetic influences on hangover across diverse representations of the hangover phenotype. Forty-five and 40% of the variance in past-year *hangover frequency* was attributable to genetic factors among men and women, respectively. We fit a bivariate biometric model to investigate whether the genetic contribution to hangover frequency was attributable to familial influences on the frequency of drinking to intoxication. Results indicated that the vast majority (75-86%) of the genetic variance in hangover frequency overlapped with familial contributions to past-year intoxication. We defined *hangover susceptibility* as the residual variance in hangover frequency after taking into account individual differences in the frequency of intoxication. A genetic factor accounted for 16% and 24% of this residual variance in women and men, respectively. Finally, we operationalized *hangover resistance* as a report of zero past-year hangovers despite having drunk to intoxication at least once during that period. Latent genetic influences accounted for 43% of the variance in this phenotype, and there was not a significant sex difference or overlap with contributions to individual differences in past-year intoxication.

Future work is needed to identify specific genes that may contribute to hangover susceptibility and resistance. Existing association studies implicate variants of genes coding for enzymes involved in the alcohol metabolism pathway, finding they account for 2.5-9.5% of the variance in perceived hangover sensitivity [16, 17]. In the current study, heritability estimates for hangover susceptibility and resistance were higher than this, potentially suggesting a broader set of genes is involved. This conclusion must be advanced cautiously, however, owing to the wide

confidence intervals around the heritability estimates and substantial differences between prior association studies and the current work in terms of sample composition and hangover assessment. Other genes associated with individual differences in level of response to alcohol may represent worthy candidates [32]. Laboratory investigations have demonstrated that individuals who report more intense acute subjective intoxication to an alcohol challenge also report more severe hangover symptoms when blood alcohol concentrations subsequently decline [6, 33]. Self-reports of diminished sensitivity to alcohol effects have also been associated with increased likelihood of hangover occurrence in studies of naturalistic drinking episodes [24, 25]. Finally, because the intensity of hangover symptoms has been shown to be correlated with circulating levels of cytokines and acute-phase proteins [14, 34, 35], genes involved in inflammatory processes may represent promising candidates for future association studies investigating hangover susceptibility and resistance [36].

Several limitations should be acknowledged. We relied on retrospective reports of hangover and intoxication frequency, so reporting bias or forgetting could contribute error to the analyses. It was reassuring that there was evidence for good test-retest reliability for measures of intoxication frequency, hangover frequency, and the hangover resistance classification. The hangover susceptibility and resistance phenotypes were defined in a manner consistent with past practices in hangover research, but alternative vulnerability assessments might be desirable in future investigations. Comparison of the findings between the two vulnerability indices is complicated by their differing direction (i.e., emphasis on sensitivity vs. robustness to alcohol effects) and the fact that the hangover resistance phenotype could only be analyzed in the 58% of the sample who had drunk to intoxication at least once in the past year. In theory, an alcohol challenge design would permit assessment of individual differences in hangover vulnerability

with greater precision among all participants. However, conducting a high-dose alcohol challenge study with an observation period long enough to permit emergence of hangover symptoms requires a great deal of time and resources, and may not be feasible in conjunction with the logistical challenges already inherent in twin or family studies. An alternative strategy for genetic epidemiology may be to survey participants more directly about the intensity of hangover symptoms they would expect to experience at a given level of alcohol consumption [16, 17]. An alcohol challenge design may be more tractable for investigating associations between indices of hangover vulnerability and measured candidate genes. Finally, the current study did not include measures of participant characteristics theoretically related to hangover, such as level of response to alcohol, impaired control over drinking, or biomarkers of inflammation. Extensions of the current work to include these kinds of measures in multivariate, genetically-informed designs might substantially advance our understanding of the etiologic processes giving rise to various hangover phenotypes.

In conclusion, the results reinforce the assertion that measures tapping hangover frequency and sensitivity should be interpreted differently, with hangover frequency representing the broader construct. The observation of significant heritability for the narrower hangover susceptibility and resistance phenotypes suggests there are genetically-influenced individual differences in the likelihood of experiencing a hangover at a given level of alcohol use. Existing evidence suggests that polymorphisms related to alcohol metabolism, subjective response to alcohol, and inflammatory processes may represent promising candidates for use in future association studies.

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Figure captions

Figure 1.

Diagram of a Cholesky decomposition of genetic and unique environmental influences on the frequency of intoxication and hangover (to simplify presentation, only one twin from a pair is shown). The 'x' path represents genetic influences on intoxication frequency that also influence hangover, the 'w' path represents unique environmental influences on intoxication frequency that also influence hangover. The 'y' path represents residual genetic variation in hangover that is not shared with the frequency of intoxication (i.e., hangover susceptibility), and the 'z' path represents residual unique environmental variation in hangover that is not shared with the frequency of alcohol intoxication.
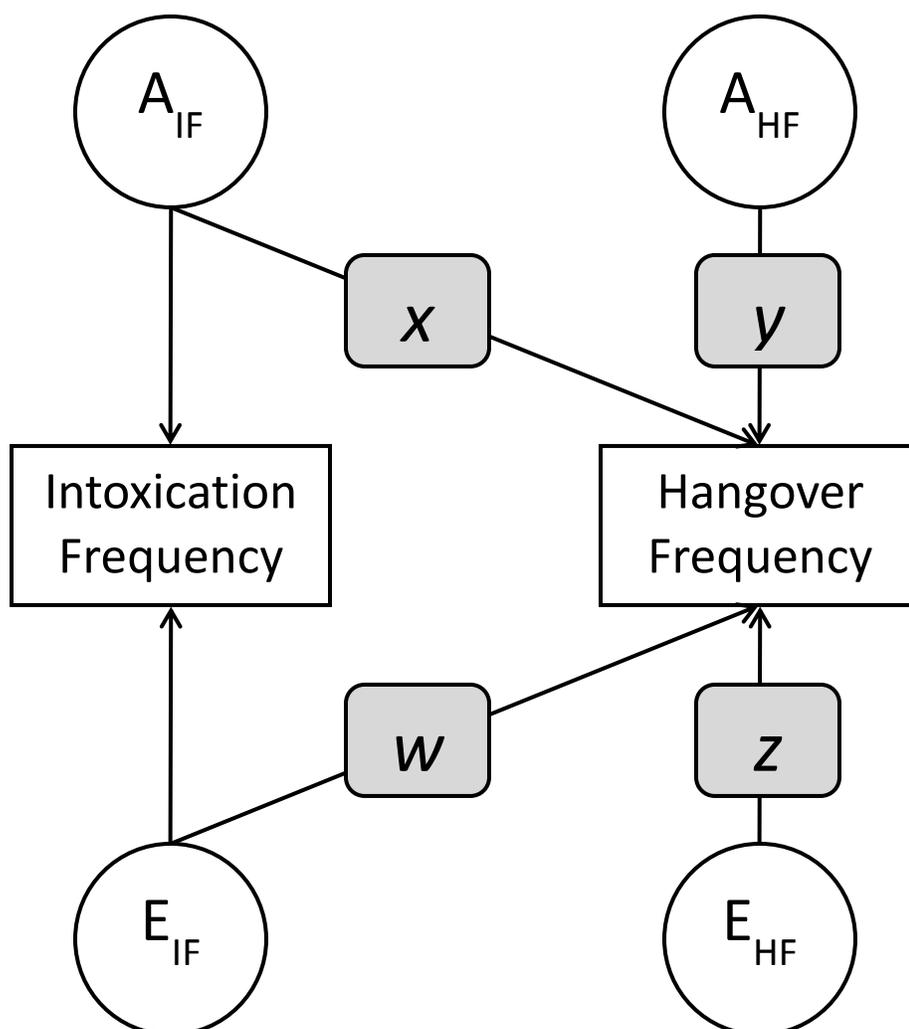
Table 1. Twin correlations for past-year hangover					
	Monozygotic		Dizygotic		
	Men	Women	Men	Women	Opposite Sex
	N = 323 pairs	N = 461 pairs	N = 208 pairs	N = 326 pairs	N = 375 pairs
Within-trait correlations					
Hangover frequency	**.44**	**.41**	**.27**	**.17**	.09
Hangover resistance	**.44**	**.43**	-.01	.36	.08
Intoxication frequency (IF)	**.51**	**.35**	**.31**	.10	.09
Cross-trait correlations					
IF with hangover frequency	**.43**	**.32**	**.25**	.16	.08
IF with hangover resistance	**-.20**	-.10	-.19	-.21	-.01

Note: IF = intoxication frequency; correlations in bold are significantly greater than zero at $p < .05$. Sample sizes represent the number of complete twin pairs, individual twins from 1,110 incomplete pairs were also included in analyses.

Table 2. Proportion of variation in hangover explained by additive (A), non-additive genetic (D), and unique environmental (E) influences.

Hangover index	Full sample			Men			Women		
	A	D	E	A	D	E	A	D	E
	Full models								
Frequency	.43	.00	.57	.45	.00	.55	.30	.11	.59
95% CI	.37, .49	.00, .02	.52, .62	.37, .53	ne	.47, .63	0.0, .70	0.0, .53	.51, .67
Resistance	.22	.22	.56	.02	.41	.57	.45	.01	.54
95% CI	.00, 1.0	.00, 1.0	.35, .78	.00, 1.0	.00, 1.0	.27, .88	.00, 1.0	.00, 1.0	.24, .81
	Reduced models								
Frequency	.43	---	.57	.45	---	.55	.40	---	.60
95% CI	.38, .48	---	.52, .62	.37, .53	---	.47, .63	.33, .48	---	.52, .67
Resistance	.43	---	.57	.46	---	.54	.40	---	.60
95% CI	.22, .63	---	.37, .78	.16, .75	---	.25, .84	.10, .69	---	.31, .90

Note: A = additive genetic influences, D = non-additive genetic influences, E = unique environmental influences, CI = confidence interval, ne = not estimable.

	Intoxication frequency		Hangover frequency					
			Total variation		Portion shared with intoxication frequency		Portion unshared with intoxication frequency: susceptibility	
	A	E	A	E	A	E	A	E
Men	.55	.48	.43	.57	.33	.23	.11	.34
95% CI	.48, .61	.39, .52	.36, .51	.49, .64	.25, .40	.16, .29	.06, .16	.29, .39
Women	.41	.59	.40	.60	.34	.29	.06	.31
95% CI	.34, .48	.52, .66	.32, .48	.53, .68	.28, .42	.26, .32	.03, .09	.25, .38

Table 3. Results of bivariate biometric model fitting of frequency of intoxication and hangover.

Note: A = additive genetic influences, E = unique environmental influences, CI = confidence interval

Table 4. Results of bivariate biometric model fitting of frequency of intoxication and hangover resistance.

| | Intoxication frequency | | Hangover resistance | | | | | |
| | | | Total variation | | Portion shared with intoxication frequency | | Portion unshared with intoxication frequency | |
	A	E	A	E	A	E	A	E
Men	.56	.44	.38	.62	.07	.00	.32	.62
95% CI	.47, .65	.35, .53	.10, .67	.33, .91	-.02, .15	-.01, .01	.03, .60	.33, .90
Women	.37	.63	.45	.55	.07	.00	.38	.55
95% CI	.30, .44	.56, .70	.15, .74	.26, .85	-.04, .18	-.01, .02	.08, .67	.26, .84

Note: A = additive genetic influences, E = unique environmental influences, CI = confidence interval