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Sex Differences in the Heritability of Alcohol Problems

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Genetic factors may have a role in defining more coherent clinical phenotypes and subtypes in the DSM-V. Research has demonstrated that there are gender differences in the patterns of alcohol consumption, specific symptom endorsement, withdrawal effects, and rates of alcohol use disorders (AUD). We examined the sex-specific heritability of diagnostic symptoms for alcohol-related problems in a community-based sample of twin pairs (males: n = 519; females: n = 613) using a biometrical analytic strategy to estimate the genetic and environmental components of AUD symptoms. Five of the seven symptoms of alcohol problems demonstrated sex-differences in heritability. Three of the seven symptoms examined had significant heritability in female twins only: "increased risk of injury or harm," "emotional problems related to drinking," and "the desire to drink." In males, a different pattern was observed, with four of the seven examined symptoms demonstrating heritability: "Increased chance of injury or harm," "spending more time using alcohol or getting over its effects," "using larger amounts for longer periods of time than intended," and "the need to use more alcohol to get the same effect." These data suggest that alcohol problems in females and males may be etiologically distinct, and that diagnostic criteria and therapeutics might be enhanced if these sex differences were taken into consideration. (Am J Addict 2008;17:319–327)

INTRODUCTION

Since the time of Sir Francis Galton, the twin method has been widely used to estimate both the heritable and environmental components of a condition. This approach takes advantage of the fact that monozygotic twins share the same genetic make-up, while dizygotic twins are genetically no different than other biological siblings in that they share 50% of their genes in common. Highly heritable conditions show substantial concordance among monozygotic twins due to their shared genetic structure, but considerably less concordance is seen among dizygotic twins. Highly environmental conditions show high rates in both monozygotic and dizygotic twins who are exposed to the high risk environments. In both cases, it is assumed that the co-twin's rearing environment is the same, having grown up in the same house. Beginning in the 1970s, a mathematical modeling approach to disentangling genetic and environmental effects in twins emerged.[1] This approach has become known as the "biometrical model" and it uses twin data to estimate the variation in a trait that may be attributed to genetic factors, shared environmental factors, and unique individual environmental exposures. This biometrical modeling approach is now fundamental to twin research, where the goal is to understand the heritability of given traits and the sources of environmental influence.

Alcohol Dependence (AD), as a clinical syndrome, is generally regarded as a complex disorder of which the etiology is posited to be the result of an interaction between genetic and environmental influences. Genetic risk for AD is estimated to be within the range of 50%–60%,[2] with the remainder being attributed to environmental effects. These estimates have been reported to be similar in both sexes,[3–5] although differences in drinking behaviors between men and women have been identified.[6–8] As a consequence of this significant hereditability, the search for the genes contributing to this risk continues. However, initial findings of some studies have not been successfully replicated in follow-up investigations. Buck[9] has suggested that the inconsistencies in these findings are due to "phenotypic heterogeneity, genetic heterogeneity, and gene-environment interactions. For example, Hasin and Grant[6] have recently demonstrated that alcohol dependence and alcohol abuse may be discretely different phenotypes with different associated risk characteristics. The diagnostic symptoms used to delineate the presence or absence of syndromal alcohol use disorders(AUDs) may be an important source of phenotypic heterogeneity.

As the research agenda for DSM-V is currently being mapped out, it is useful to examine the heritabilities of individual DSM-IV AUD criteria because of both the clinical and research implications of such data. Genetic factors may have a role in defining more coherent clinical phenotypes

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and subtypes in the new taxonomy.[10] On the other hand, an influential diagnostic criterion that is common, but is neither exclusive to a diagnostic group nor substantially heritable, may result in a less specific diagnostic categorization and increase erroneous assumptions about it falling within a "spectrum" of other conditions.

To date, there have been few reports in the twin literature examining genetic influences on the individual symptoms from which the alcohol abuse and dependence diagnoses are derived. Johnson, van den Bree and Pickens used the Diagnostic Interview Schedule Version III (DIS-III) to examine alcohol-dependent male twins ($n = 113$).[11] These subjects were recruited from treatment settings, and as such, were not representative of community-dwelling individuals with AD. They used 17 AD items from the DIS-III that were categorized as genetic or environmental by evaluation of the MZ/DZ differences in concordance.[12] Factor analysis was used to assess the fit of each item to a latent construct of genetic or environmental cause. The results indicated that the following symptoms loaded on the single latent trait for a genetic scale: job trouble because of drinking and/or lost job; alcohol-related health problems and/or continued drinking despite health problems, drinking binges lasting at least a couple of days, and needing a drink in the morning just after waking.[11] These "genetic" symptoms comprise phenomenological domains that include alcohol-related psychosocial dysfunction, pathological patterns of use, and acute withdrawal symptoms. "Environmental" symptoms also included those associated with aspects of alcohol-related psychosocial dysfunction, withdrawal symptoms, and concerns over drinking behavior and loss of control.

Slutske[13] used data collected from 3,356 male twin pairs, both of whom had served in the military during the Vietnam war (Vietnam Era Twin Registry), with the primary objective of replicating the findings of Johnson. This group reported that the advantages of studying veterans included their nearly ubiquitous exposure to alcohol, their higher rates of alcoholism than the non-veteran population, and a community-based cohort sample rather than one ascertained through treatment settings. Their findings indicated that nine symptoms were consistently classified as genetic and six symptoms were consistently non-genetic. The nine symptoms classified as genetic included: "binging for a few days;" "drinking just after getting up," "having seven drinks a day for at least two weeks," "a couple of months of drinking seven drinks at least one day a week;" "the presence of withdrawal symptoms" (ie, DTs, seizures), "family member complaints that the proband was drinking too much," "inability to stop drinking," "physician diagnosis of a drinking problem," and "fighting when drinking." It is noteworthy that the classification of these symptoms differed substantially from those identified earlier by Johnson.[11]

As pointed out by McGue, our current estimates of the heritability of alcoholism may "obscure the existence of a subset of alcoholism symptoms that are strongly genetically influenced". Our goal herein is to define those heritable alcoholism symptoms. This study is an extension of the prior research that applied biometrical analyses to twins in an effort to identify the genetic and environmental influences on the criterion symptoms for AUDs.[11,13,15] A strength of this effort is the use of an independent and representative community sample of twins accrued through the National Survey of Midlife Development in the United States (MIDUS).[16] Whereas the aforementioned earlier studies were limited to examining the heritability of alcohol symptoms only in males, an additional strength of this study is the inclusion of female twins. Here, we investigate alcohol use disorder symptoms independently in male and female probands in order to identify the most useful clinical phenotypes for the genetic investigations of alcoholism in a gender-specific fashion.

METHODS

Sample

The sample consisted of twins who participated in the National Survey of Midlife Development in the United States (MIDUS),[16] an interdisciplinary exploration of predictors and consequences of midlife development covering social, psychological, and physical health issues. The twin design screened 50,000 nationally representative households. The households were drawn from representative random-digit-dial samples of non-institutionalized English speaking adults and were separate from the general MIDUS sample ascertainment. Those households with a twin were then contacted to determine their willingness to participate in the survey and to provide contact information about their co-twin. A total of 998 twins pairs ($n = 1,996$) were recruited.[16] Subjects who reported never having had a drink or drinking less than one drink a day during the year that they drank the most ($n = 1652$), subjects for whom data was missing for their corresponding twin, and data from triples, quads etc., were excluded from these analyses. After exclusion of non-drinkers and those with low exposure, 511 twin pairs ($n = 1132$) were included in the analyses. The endorsement rates of those with a co-twin and those excluded because of missing twin data were compared, and no significant differences ($p > 0.05$) were found in any of the seven symptoms examined. The 1,132 individual twins used in the analysis consisted of 519 males and 613 females. (The odd number of males and females results from the inclusion of mixed sex twins in the study.) The mean age for males was 44.13 (SD 11.54) years. The ages ranged from 25 to 74 years of age for males and 25 to 73 years of age for females (see Table 1). Zygosity diagnosis included "whether the twins had the same eye color, natural hair color, and complexion, whether individuals mistook them for each other when they were young; and, whether they had ever undergone testing or been told by a doctor whether they were genetically identical or fraternal."[16] The twins were asked to provide a cheek scraping to provide DNA to determine zygosity, although, to our knowledge, the MIDUS investigators have not validated zygosity by this method.

TABLE 1. Demographics

Gender	Male	Female	Total sample
Age (SD)	44.55 (11.67)	43.78 (11.44)	44.13 (11.54)
Monozygotic twins	232	254	486
Dizygotic twins	287	359	646
Same sex dizygotic twins	144	216	360
Mixed sex dizygotic twins	143	143	286
Total	519	613	1132

Survey Questions

The twin survey assessed 2,223 variables containing all of the general MIDUS questions and additional questions about childhood and adult experiences of being a twin. This study is focused on the questions (see Table 2) from the general MIDUS survey completed by the twin pairs assessing alcohol use and associated behaviors. The questions approximate many, but not all, of the DSM-IV symptoms for alcohol abuse and dependence. Although it would be possible to derive a diagnosis of abuse or dependence from this data, it would be an incomplete or a crude estimate because of the missing DSM-IV symptoms. Two of the questions provided ordinal data ("using larger amounts longer than intended," and "suffering the effects or after-effects of alcohol at home or work"), and were dichotomized for the purposes of these analyses into "ever occurred" or "never occurred" in the last 12 months.

Statistical Analysis

Biometrical Model

The biometrical model of decomposition of variance is the basis of the analytic strategies that we employed. The method parallels those used by Maes in the examination of dichotomous variables.[17] Tetrachoric correlations were determined using Mx (entered as contingency tables) for twin pairs without missing data, as all of the symptoms were dichotomous.[18] The assumption of an underlying normal distribution with a threshold for the endorsement of a criterion facilitated the variance component estimation of additive genetic (A), shared environmental (C), and unique environmental (E) variance using maximum likelihood. The solutions are also dependent on three further assumptions:

TABLE 2. MIDUS Survey Questions related to alcohol use (Inital phone question used for inclusion)

The next questions are about alcoholic beverages. How old were you when you had your first drink, not counting a sip of someone else's drink?

MIDUS questions related to criteria for alchol abuse and dependence (questions on the mail portion of the survey	*DSM-IV related criteria*
Were you ever, during the past 12 months, under the effects of alcohol or feeling its after-effects in a situation which increased your chances of getting hurt	**Alcohol abuse** Recurrent use when physically hazardous
Did you ever during the past 12 months have any emotional or psychological problems from using alcohol?	**Alcohol abuse and dependence** Continued use despite social or interpersonal problems caused by or exacerbated by use
Did you ever, during the past 12 months, have such a strong or urge to use alcohol that you could not resist it or could not think of anything else?	**Alcohol dependence** Persistent desire or repeated unsuccessful attempts to quit or cut down on alcohol use
Did you have a period of a month or more during the past 12 months when you spent a great deal of time using alcohol or getting over its effects?	**Alcohol dependence** Much time spent obtaining, using or recovering from the effects of alcohol.
Did you ever, during the past 12 months, find that you had to use more alcohol than usual to get the same effect or that the same amount had less effect on you than before?	**Alcohol dependence** Tolerance
During the past 12 months, how many times did you use larger amounts of alcohol than you intended to when you began, or used them for a longer period of time than you intended to? (Converted to ever or never for analysis)	**Alcohol dependence** Need to consume more to obtain the same effect: decreased effect at the same dose
In the past 12 months, how many times have you been under effects of alcohol or suffering their after-effects while at work or school, or while taking care of children? (Converted to ever or never for analysis)	**Alcohol abuse** Frequent intoxication leading to failure to fulfill obligations at school, work, home

1. the known difference in the proportion of shared genes between twins (100% for monozygotic [MZ] and 50% for dizygotic twins [DZ]);
2. an assumption of equal effects of the environment on MZ and DZ twins; and
3. non-assortative mating.

Initially, the effects of gender were determined using the biometrical model, which was extended from a two-group (MZ/DZ) analysis to five-groups female (MZ/DZ), male (MZ/DZ), and mixed-sex DZ twins. This was accomplished using a five-group model script modified from an existing Mx script.[19] These analyses provide estimates and fit indices for the full ACE model and the 11 potential nested models' testing of equal and unequal variance for heritability environmental effects and gender (see Table 3). For models indicating no difference in gender, a two-group MZ/DZ analysis was completed using all available twins. Where the initial analysis (five groups) indicated gender differences, further gender-specific two group (MZ/DZ) analyses were completed. In these analyses, the mixed sex DZ twins were dropped to provide a more direct test of gender effect.

Model Fitting

The five-group models (examining gender differences) and subsequent two-group models (independent male (MZ/DZ) and female (MZ/DZ) for those symptoms demonstrating gender differences) were examined for level of fit using the same criteria. In the two-group (gender-specific) models for each symptom, the full model estimating all three components of variance (ACE model) was followed by fitting for the three (nested) submodels AE, AC, and E. Models were evaluated using fit indices provided by Mx.[18] Similarly, the five-group models (examining gender differences) examined full models and nesting as well as gender contrasts (models listed in Table 3). The best fitting model for each analysis was selected employing the chi-squared statistic (χ^2), its associated degrees of freedom, the RMSEA, and the Akaike's Information Criterion (AIC) (χ^2-2df).[20] The lowest AIC indicated the best compromise of the most parsimonious and best-fitting model,[17,18] while the RMSEA provided further confirmation of fit.

Summary

The biometric model uses known differences in the proportion of genes that monozygotic and dizygotic twins share to provide information on the genetic and environmental influences for each symptom explored. Each symptom will have varying proportions (from 0 to 100%) of its variance contributed by genes, the family (shared environment), and environmental experiences not shared by each twin. Current thinking suggests that genes are rarely fully independent of the environment in their actions. A gene on DNA is translated through a complex process where the environment moderates which protein or shape of a protein is produced, which determines the phenotypic (symptom) behavior. Thus, it is pragmatic that a symptom could have a portion of its etiology from the two forms of the environment and genetics.

The selection of the best model among competing models is accomplished using techniques developed in structural equation modeling and is further extended to two groups (gender in this case). There are several models fitting criteria, with the three most commonly applied in twin analyses provided here.

RESULTS

Biometrical Model Fitting

The seven symptoms of alcohol-related problems and their endorsement rates are shown in Table 4. The results of the five-group model (gender differences) indicated variance differences in five of seven symptoms examined; the most parsimonious model is presented in Table 5. Subsequent two-group models, variance estimates, confidence intervals, and fit criteria are presented in Table 6. Models for both the ACE model (full model) and the "best fit" are presented separately for females and males where the five-group analyses have indicated gender differences. As may be noted, Table 6 demonstrates sex differences in the heritability of five of the seven symptoms examined. Three of the seven symptoms examined had significant heritability in female twins only. "Increased risk of injury or harm" (71%), "emotional problems related to drinking" (53%), and "the desire to drink" (63%), all demonstrated parsimonious AE models. "Using larger amounts for longer periods of time than intended" (62%) also demonstrated an AE model, but had the same heritability on both males and females. Variances for the remaining diagnostic symptoms were attributable to the influences of unshared (non-familial) environment in female twins. These include "spending more time using alcohol or getting over its effects." and "the need to use more alcohol to get the same effect." "Using alcohol or recovering from its effects at work, school or while caring for children" was also attributable to the influence of unshared (non-familial environment) but the same in both genders.

A different pattern was observed in males, with four of the seven examined symptoms demonstrating heritability. "Increased chance of injury or harm" (49%), "spending more time using alcohol or getting over its effects" (79%), "using larger amounts for longer periods of time than intended" (48%), and "the need to use more alcohol to get the same effect" (48%) had a heritable component to their variance (AE models) that differed from their female counterparts. The environmentally mediated CE model was most parsimonious for "emotional problems related to drinking" (53%) in men. Finally, "the desire to drink" (in males) and "using alcohol or recovering from its effects at work, school or while caring for children" (in both males and females) variances were attributable to the unique environment (E).

Impact of Age and Symptom Duration:

Individuals with early pathological consumption might not be present in the older age cohort of the survey because the

TABLE 3. Five group variance covariance models used to determine gender differences

1.	Different prevalence for males and females, ACE for males for females allowing for free estimation for mix sex twins
2.	Same prevalence for males and females, ACE for males for females allowing for free estimation for mix sex twins
3.	Same prevalence for males and females, fixed estimation at 0.5 for mix sex twins
4.	Same prevalence for males and females, ACE fixed estimation at 0.5 for mix sex twins
5.	Same prevalence for males and females, AE with fixed estimation at 0.5 for mix sex twins
6.	Same prevalence for males and females, CE with fixed estimation at 0.5 for mix sex twins
7.	Same prevalence for males and females, E with fixed estimation at 0.5 for mix sex twins
8.	Different prevalence for males and females, ACE with fixed estimation at 0.5 for mix sex twins
9.	Different prevalence for males and females, ACE fixed estimation at 0.5 for mix sex twins
10.	Different prevalence for males and females AE with fixed estimation at 0.5 for mix sex twins
11.	Different prevalence for males and females, CE with fixed estimation at 0.5 for mix sex twins
12.	Different prevalence for males and females, E with fixed estimation at 0.5 for mix sex twins

adverse effects of risky drinking could have resulted in their early deaths. Further, the number of symptoms present may change with age resulting in some systematic bias in the sample. The relationship between the alcohol symptom count and age was explored using a Pearson correlation in both men (rho $= -0.19, p > 0.05$, n $= 689$) and women (rho $= -0.21$, $p > 0.05$, n $= 797$) and suggests age has a very humble effect on alcohol symptom counts. The duration of pathological use is not present in this data set and would be an important future consideration in the replication of this study.

DISCUSSION

The study provides provisional support for sex differences in the heritability of specific symptoms of alcohol problems referable to the DSM-IV criteria for AUDs. For female twins, five out of the seven studied symptoms were found to have a heritable component. These tended to focus around alcohol-related harm, craving, and loss of control. The two heritable symptoms found in males and shared by both sexes appear to represent intermediate phenotypes of loss of control or compulsive drinking and alcohol-related harm. As noted by Hasin and Grant, these symptoms appear to be more specific to the syndrome of alcohol dependence than to alcohol abuse.[6]

At the clinical level, these results suggest that females from multiplex families with alcohol problems might present different symptom profiles than males or females without familial alcoholism. Furthermore, those with heritable symptoms might differentially benefit from pharmacotherapies and specific psychotherapies than those with more environmental manifestations. Clinical trials of such interventions for alcohol problems in males and females should take into account these

TABLE 4. Diagnostic criteria and endorsement rate by gender

Criteria	Female endorsement	Female total	Female rate	Male endorsement	Male total	Male rate
Increase chance of harm	38	613	6.20%	81	519	15.61%
Emotional problems	13	607	2.14%	22	522	4.21%
Desire to use	12	314	3.82%	18	522	3.45%
Time using or recovering	10	613	1.63%	19	521	3.65%
Use more to get effect	11	611	1.80%	21	521	4.03%
Larger or longer use	11	419	2.63%	8	301	2.66%
Use at work, school, or while caring	8	557	1.44%	8	455	1.76%
			Endorsement rates by gender and zygocity			
	Male MZ	Male DZ	Female MZ	Female DZ	Male-Female DZ	Female-Male DZ
Increase chance of harm	13.27%	21.26%	7.63%	5.88%	16.24%	12.78%
Emotional problems	4.19%	5.48%	3.32%	2.39%	2.99%	2.01%
Desire to use	4.19%	4.76%	4.19%	2.37%	2.26%	0.00%
Time using or recovering	4.19%	6.21%	2.01%	1.90%	0.00%	0.79%
Use more to get effect	3.70%	5.48%	1.60%	2.39%	3.08%	2.01%
Larger or longer use	7.14%	0.85%	2.86%	1.39%	6.02%	2.08%
Use at work, school or while caring	1.60%	3.94%	1.75%	0.51%	3.23%	0.74%

TABLE 5. Best fitting models five group biometric models to determine the effects of gender

Question	Best fit model	Chi square	DF	AIC	RMSEA
Increase chance of harm	Genders Differ AE Model	18.35	15	−11.64	0.03
Emotional problems	Genders Differ AE Model	11.84	15	−18.16	0.00
Desire to use	Genders Differ E Model	22.64	16	−9.35	0.04
Time using or recovering	Genders Differ AE Model	19.28	15	−10.71	0.03
Use more to get effect	Genders Differ E Model	16.94	16	−15.07	0.024
Larger or longer use	Genders Same AE Model	25.51	16	−6.49	0.055
Use at work, school, or while caring	Genders Same E Model	21.94	17	−12.06	0.04

potential subtypes of heritable symptom presentations. These sex differences in symptoms might also inform the DSM-V process, wherein an effort is being made to take into account sex differences in the manifestations of psychiatric and substance use disorders.[10] Researchers often are faced with the choice of using the presence or absence of a disorder or symptom counting as measures of phenotype. This lumping strategy may come with too large a cost in the exploration of genetic influences in complex disorders. Twin data provide a method for narrowing the phenotype to those symptoms or behaviors associated with genomic differences, thus improving the sensitivity and reducing signal to noise difficulties that are commonly encountered in genetic reports.[21] Our results suggest that potentially informative phenotypes could include subject groupings based on sex and heritable diagnostic symptoms.

The sources of sex differences in heritability estimates of individual AUD symptoms have not been elucidated. Research has demonstrated that there are sex differences in the patterns of alcohol consumption, specific symptom endorsement, withdrawal effects, and in rates of AUDs,[22] but that these differences are less apparent for younger cohorts.[23] Some brain structures, such as the inferior frontal gyrus, show sex differences in terms of white and gray matter, and it has been postulated by Blanton and colleagues[24] that these structural differences may arise as a result of sex steroid effects on brain development. For example, testosterone concentrations may inhibit synaptic pruning and account for greater inferior frontal volumes in boys, leading to more impulsive behaviors, including high-risk drinking. Sex-specific patterns of problem behaviors have been documented in children of alcoholics, which suggests transmissible, if not genetic, variations.[25] Such potentially heritable behavioral propensities could interact with hazardous levels of alcohol consumption, producing a differential pattern of adverse consequences. Research using animal models has suggested that gonadal steroids and stress hormones might interact in a manner that yields significant differences between the sexes in behavioral responses and neuroadaptations to chronic alcohol consumption and withdrawal.[26] Other work has suggested that genetically determined alcohol dehyrogenase (ADH) activity might explain differential patterns of drinking. For example, individuals who carry the most active ADH forms are protected against alcoholism. When male and female rats are offered alcohol, females showed 70% higher hepatic ADH activity and displayed 60% lower voluntary ethanol intake than males, suggesting a biological basis for differential consumption and behavioral effects.[27]

This study differs significantly from those previously reported in the criterion items utilized, the method of sample ascertainment, sample size, and the analytic strategy and in sex of the probands. As such, it is difficult to make direct comparisons to the earlier works of Slutske et al.[13] and Johnson et al.[11] who also used a "candidate symptom" approach to examine the heritability of diagnostic symptoms, but in male twins only and with a differing data collection method. That being said, Johnson et al. found seven symptoms to be heritable and 14 symptoms to be "environmental," while Slutske and colleagues failed to replicate the findings of Johnson and colleagues. In their report, 13 symptoms were found to be "genetic," and only three were shared in common with the Johnson study. The symptoms found to be heritable in both prior studies related to binge drinking (two items) and early morning consumption to avoid withdrawal symptoms. On the other hand, the Slutske et al. report found consistent heritability for withdrawal-related symptoms, binge or heavy drinking patterns, and loss of control. Not surprisingly, alcohol-associated harm and health problems, as well as "blackouts," which are pharmacological effects of alcohol, were found not to be heritable. Our study only shares agreement with the previous studies to the extent that aspects of drinking patterns and loss of control were found to be heritable in men and women.

Johnson and colleagues[11] studied 113 all-male twin pairs that were recruited from treatment settings. Slutske et al.[13] investigated Vietnam-era male veterans with a substantially larger sample than we were able to employ in our analyses. We concur with their cautionary comment concerning the interpretation of findings such as ours and that of Johnson and colleagues, given the limited sample sizes and large confidence intervals in both studies.

There are several other limitations of this study. First, there was secondary data originally generated for purposes other than examining the genetic liability of alcohol use disorders. The design did not provide enough data to develop a reliable diagnosis of alcohol abuse or dependence as not all DSM-IV diagnostic symptoms were assessed in the survey in the exact manner as they appear in the diagnostic manual. There

TABLE 6. Results of biometrical analyses of AUD diagnostic symptoms in female and male twins

Diagnostic Criteria	Sex	Chi square	Df	*p*-value	AIC	RMSEA	Model	Additive genetics	CI	Shared environment	CI	Unique Environment	CI
Increase chance of harm	Female	7.73	3	0.05	1.73	0.74	ACE	0.71	0.00–0.91	6.13E–13	0.00–0.79	0.28	0.09–0.68
		7.73	4	0.10	−0.27	0.63	AE	0.71	0.34–0.9	0.00	na	0.29	0.088–.66
	Male	6.33	3	0.10	−0.33	0.71	ACE	0.49	0.00–.78	8.47E-15	0.00–0.47	0.51	0.22–0.90
		6.33	4	0.18	−1.67	0.58	AE	0.49	0.10–0.78	0.00	na	0.51	0.022–0.90
Emotional problems	Female	2.61	3	0.46	−3.39	0.02	ACE	0.53	0.00–0.90	4.5978E-13	0.00–0.80	0.47	0.10–1.00
		2.61	**4**	**0.63**	**−5.39**	**0.00**	**AE**	**0.53**	**0.00–0.90**	**0.00**	**na**	**0.47**	**0.10–1.00**
	Male	1.57	3	0.67	−4.42	0.00	ACE	0.04	0.00–0.89	0.47	0.0–0.82	0.49	0.11–0.98
		1.57	**4**	**0.81**	**−6.42**	**0.00**	**CE**	**0.00**	**na**	**0.50**	**0.02–0.82**	**0.50**	**0.18–0.98**
Desire to use	Female	3.57	3	0.31	−3.26	0.02	ACE	0.67	0.00–0.96	2.84E-1	0.00–0.84	0.33	0.04–1.00
		3.57	**4**	**0.47**	**−4.43**	**0.00**	**AE**	**0.61**	**0.00–0.96**	**0.00**	**na**	**0.39**	**0.04–1.00**
	Male	5.04	3	0.17	−0.96	0.39	ACE	2.55E-14	0.00–0.60	9.93E-16	0.00–0.50	0.99	0.40–1.00
		5.04	**5**	**0.41**	**−4.97**	**0.02**	**E**	**0.00**	**na**	**0.00**	**na**	**1.00**	**1.00–1.00**
Time using or recovering	Female	2.41	3	0.49	−3.59	0.01	ACE	2.96E-14	0.00–0.81	3.54E-16	0.00–0.68	0.99	0.19–1.00
		2.41	**5**	**0.79**	**−7.59**	**0.00**	**E**	**0.00**	**na**	**0.00**	**na**	**1.00**	**1.00–1.00**
	Male	2.58	3	0.46	−3.41	0.01	ACE	0.74	0.00–0.97	0.06	0.00–0.85	0.20	0.03–0.71
		2.58	**4**	**0.63**	**−5.41**	**0.00**	**AE**	**0.79**	**0.33–0.97**	**0.00**	**n.a.**	**0.21**	**0.03–0.67**
Use more to get effect	Female	4.60	3	0.20	0.141	0.06	ACE	2.55E-14	0.00–0.81	4.34E-15	0.00–0.73	0.999	0.19–1.00
		4.60	**5**	**0.47**	**−5.4**	**0.04**	**E**	**0.00**	**na**	**0.00**	**na**	**1.00**	**1.00–1.00**
	Male	5.20	3	0.16	−0.80	0.038	ACE	0.48	0.00–0.90	3.57E-15	0.00–069	0.99	0.10–1.00
		5.20	**4**	**0.27**	**−2.79**	**0.026**	**AE**	**0.48**	**0.00–0.90**	**0.00**	**na**	**0.52**	**0.0.10–1.00**
Larger or longer use Same run one gender	No gender difference	4.77	3	0.19	−1.23	0.03	ACE	0.62	0.00–0.96	1.21E-15	0.00–0.60	0.38	0.04–1.00
		4.77	**4**	**.25**	**−3.27**	**0.007**	**AE**	**0.62**	**0.00–0.96**	**0.00**	**na**	**0.38**	**0.04–1.00**
Use at work, school or while caring run as one gender	No gender difference	10.27	3	0.016	4.27	0.76	ACE	5.31E-14	0.0–0.81	1.81E-14	0.0–0.59	1.00	0.19–1.00
		10.27	**5**	**0.07**	**2.73**	**0.42**	**E**	**0.00**	**na**	**0.00**	**na**	**1.00**	**1.00–1.00**

Note: **Boldface** indicates most parsimonious models.

is also a limitation in sample size such that our estimates had large and often overlapping confidence intervals. In this general population survey, there were a restricted number of subjects that endorsed symptoms of alcohol use disorders, and those without any endorsement were excluded from the analyses. However, this study *did* examine a limited number of symptoms of alcohol problems in a sample that has sufficient exposure (at least one drink a day during the year they drank the most), and found that several of these have a significant proportion of their variance rooted in genetic factors. It is also noteworthy that the sample ascertainment strategy for this survey may be biased toward those with less severe forms of alcohol-associated psychosocial consequences. Those without a phone or a home would be excluded from participation.

Finally, these analyses were conducted on the presence or absence of symptoms only during the last 12 months. Recently, Kraemer and colleagues demonstrated the bias created by using lifetime diagnoses in mixed age samples resulting in "pseudo-comorbidity. {Kraemer, 2006 # 26}" By using a narrower time-frame in these analyses, we hoped to avoid this potential source of bias.[28] That being said, it is possible that the biometrical twin analysis of lifetime data might offer a different result. Clinically, subjects move between abstinence, abuse, and dependence quite easily. There is no current research that assesses genetic or environmental contributions to these varying changes in use.[29] Future directions suggested from this study include replication in an independent twin sample with a large sample to elucidate the differential role of sex in the heritability of alcohol symptoms and examining the stability of results using lifetime versus last 12–month data. If successful, we recommend using those sex-specific symptoms with genetic loadings as a phenotype for future or secondary analyses of genetic linkage and association studies.[30]

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