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Relationships Between State and Trait Anxiety Inventory and Alcohol Use Disorder Identification Test Scores Among Korean Twins and Families: The Healthy Twin Study

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We explored heritabilities of the State and Trait Anxiety Inventory (STAI) and the Alcohol Use Disorders Identification Test (AUDIT), and associations including genetic and environmental correlations between the phenotypes among Korean twins and their families. We analyzed the data of 1,748 participants (835 men, 913 women, 656 individuals of monozygotic twins, 173 individuals of same-sexed dizygotic twins, 919 non-twin family members, age 30–79 years) from the Healthy Twin study. Heritabilities and bivariate analyses were assessed using the SOLAR package software. In the methods of generalized estimation equations, women in the 4th quartile of state and trait scores were 17% and 15%, respectively more likely to be hazardous alcohol users compared to women in the lower three quartiles ($P < .05$). However, there were no significant associations between these phenotypes in men. After adjusting for age and squared age, the heritability estimates were 0.26 in men and 0.34 in women for the state score; for the trait score, 0.35 in men and 0.31 in women; for the AUDIT score, 0.32 in men and 0.37 in women ($P < .001$). After adjusting for age and squared age, there was a significant genetic correlation between the trait score and the AUDIT score, and a significant non-genetic correlation between the state score and the AUDIT score in women, while there were no significant genetic or non-genetic correlations between these phenotypes in men. The STAI and AUDIT scores are heritable in Koreans and the relationships between these phenotypes may be inconsistent by sex.

■ **Keywords:** state anxiety, trait anxiety, alcohol, heritability, genetic correlation

It is generally assumed that anxious people tend to seek comfort in alcohol and alcohol use disorders (AUD) can cause anxiety; thus, a comorbidity between anxiety and AUD has frequently been found (Kushner et al., 1990; 1999; 2000; Pohorecky, 1991). The risk of developing one disorder given the presence of the other disorder has been two times or more in a variety of populations (Kushner et al., 1999; 2000). Three potential models that explained the comorbidity were causality between anxiety and AUD, shared etiology related to both disorders, and a hybrid model of the two hypotheses (Kushner et al., 2000). Prospective studies demonstrated that the relationship was reciprocal (Kushner et al., 1999) and specific for the subtypes of both disorders (Buckner et al., 2008; Buckner & Schmidt, 2009; Buckner & Turner, 2009; Schmidt et al., 2007). In contrast, the shared etiologic hypothesis implies that genetic or environmental factors that influence anxiety processes are associated with the development of AUD. However, the genetic or environmental relationships

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between AUD and anxiety have been rarely studied in Caucasians (Mullan et al., 1986; Tambs et al., 1997) and have not been published for Asians, to our knowledge.

The relationship between AUD and anxiety has been mainly focused on the particular types of AUD and anxiety defined using structured diagnostic interviews (Buckner et al., 2008; Buckner & Turner, 2009; Kushner et al., 1999; Schmidt et al., 2007). However, to our knowledge, no study has assessed this relationship using assessment tools for quantitative phenotypes of anxiety and AUD. Classification of specific subtypes of psychiatric phenotypes in general populations may be imprecise and may lead to disagreement across studies (Contreras, 2009). State and trait anxiety, the distinct aspects of anxiety, have been used to assess subclinical levels of anxiety using quantitative anxiety symptoms (Spielberger, 1983). As a quantitative assessment for AUD, the Alcohol Use Disorders Identification Test (AUDIT) questionnaire has been accepted as a suitable tool to identify individuals with early alcohol problems in clinical practice (Barbor, 2001) as well as the spectrum of alcohol use disorders in various settings and with diverse populations (Reinert & Allen, 2007).

State anxiety is the transitory pattern of emotions elicited by environmental stressors, including physiological arousal and symptoms of apprehension and worry, whereas trait anxiety refers to individual differences in the predisposition to respond to threatening situations and is generally considered as a personality disposition. State anxiety is primarily environmentally influenced, while trait anxiety reveals a roughly equal contribution of genetic and non-shared environmental factors (Lau et al., 2006; Legrand et al., 1999). As state and trait anxiety are distinct, the relationships between state anxiety or trait anxiety and AUD, with regard to genetic and environmental contributions, may be different. For example, state anxiety and AUD may be more likely to be environmentally linked and can be assumed to have different manifestations of stress reactivity, such as negative emotional and behavioral reactions under threatening circumstances. In contrast, trait anxiety and AUD may be more likely to be associated with genetic and environmental factors.

In the present study, we aimed to extend the previous understanding of an association between anxiety and AUD by evaluating the genetic/environmental relationships between the STAI and the AUDIT scores among Korean twins and their families. Additionally, heritability of each phenotype in this population was estimated.

Materials and Methods

Subjects Sampling and Study Design

The subjects were participants of the Healthy Twin study. Participants were not ascertained by their health status or psychiatric disorders. The Healthy Twin study is an ongoing nationwide community study and details about the overall methodology have been previously published (Sung et al., 2006). Between April 2005 and December 2007, a total of 2,278 Korean adult (age range 30–79 years of age) same-sexed twins and their first-degree adult family members were recruited. The family unit included a twin pair or a twin pair plus more than two other first-degree family members. The current analyses used data from 1,748 participants (835 men, 913 women) of the Healthy Twin study who were enrolled between April 2005 and December 2007. The subjects comprised 656 monozygotic (MZ) twins (536 paired twins and 120 non-paired twins) and 173 dizygotic (DZ) twins (138 paired twins and 35 non-paired twins), and 919 non-twin family members from 568 families. All the participants of Healthy Twin study visited one of three study centers located in the north-central (Seoul), midwest (Cheonan), and south-east (Busan) regions of South Korea to undergo a health examination that included clinical tests, biochemical tests, radiologic examinations, and physical measurements. The subjects completed a self-reported full-length questionnaire including STAI and AUDIT before visiting study centers. In the case of unanswered questions, they were asked to have these answered by research assistants. All the procedures of the Healthy Twin Study were standardized between centers through the development of a standard protocol and training of research coordinators and research assistants. Written informed consent was obtained from all participants. The study procedure was in accordance with the ethical standards of the ethics committees at the Samsung Medical Center and Busan Paik Hospital and with the Helsinki Declaration of 1975, as revised in 1983.

Measurements

The Korean version of the AUDIT (Kim et al., 1999) was administered to subjects reporting current alcohol use. Current alcohol users were defined as the participants who answered 'yes' to the following question: 'Do you currently drink alcohol?' The Korean version of the AUDIT consists of 10 questions designed to assess three conceptual domains: alcohol intake (items 1–3), dependence (items 4–6), and adverse consequences (items 7–10). The total score is calculated by summing the values of the corresponding response options and can range from 0 to 40. A previous study using the Korean version of AUDIT revealed that its sensitivity and specificity for alcohol problems, AUD, and alcohol dependence was 84–97% and 74–95% for cut-points of 12, 15, and 26, respectively (Kim et al., 1999). Hazardous alcohol use was defined when the AUDIT score was 8 or more (Barbor, 2001). The internal consistency (Cronbach's alpha) of the Korean version of AUDIT was computed as 0.89 in the present study. State and trait anxiety were assessed using the Korean version of the State-Trait Anxiety Inventory (STAI; Kim & Shin, 1978). The STAI consists of two scales that measure state or current levels of anxiety and trait, or general levels of anxiety. Each scale contains 20 items rated on a 4-point scale (Kim & Shin, 1978; Spielberger, 1983). The internal consistency

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(Cronbach's alpha) of the two scales was computed as 0.92 for state anxiety and 0.89 for trait anxiety in present study. Other data used in this study were self-reported alcohol drinking frequency, amount of consumed alcohol (g/week), smoking status, and education level.

For two thirds (400 pairs) of the twin pairs, twin pair zygosity was identified by the Amp*Fl*STR Identifier Kit (Perkin Elmer, Waltham, MA, USA) with 16 short tandem repeat (STR) markers (15 autosomal STR markers and one sex determining marker), and for the remaining twin pairs a zygosity-determining questionnaire was used. The accuracy of the zygosity questionnaire is 97% (Song et al., 2000).

Statistical Analysis

Comparisons of categorical variables and continuous variables by sex were conducted using chi-squared tests and *t* tests, respectively. Intra-class correlations within twin pairs were computed by zygosity. Associations between hazardous alcohol use and quartiles of state or anxiety scores (4th quartile vs. lower three quartiles) were assessed using the method of generalized estimation equation (GEE) after adjustment for age, education level, and smoking status. The GEE method was separately conducted by sex because there was a significant interaction between sex and quartiles of STAI scores in the association with hazardous alcohol use. These analyses were performed using SPSS, version 14.0KO for Windows [Release 14.0.2 (21 Apr 2006); SPSS Inc., Chicago, IL, USA].

Quantitative genetic analysis was separately conducted by sex using the Sequential Oligogenic Linkage Analysis Routines (SOLAR) package (http://solar.sfbrgenetics.org; Version 4.2.0; Blangero et al., 2001) to fit a variance components model for estimating the heritability and bivariate analysis. We fitted variance component models to partition the variation of the traits, STAI and AUDIT scores, into genetic and environmental components. In this model, genetic component means additive and independent genetic effects of both within and between families (σa^2). The environmental component reflects the effects of individual specific factors that are independent within family members and includes the effects of any measurement error (σe^2). In addition, the effects of unmeasured shared environmental components (σc^2) within a family were tested and added to the model if a σc^2 effect was significant. The assumption of this model is that the effects of environmental factors are common to the members of a family and the three factors have independent and additive effects on the trait variance, with the total phenotypic variance being the sum of the individual specific variance components ($\sigma p^2 = \sigma a^2 + \sigma c^2 + \sigma e^2$). Heritability was estimated as the ratio of genetic variance to total phenotypic variance ($\sigma a^2/\sigma p^2$) using maximum likelihood method. To reveal any evidence of the pleiotropy (shared additive genetic effects on a trait pair) between the STAI scores and the AUDIT scores, bivariate analyses were conducted to partition the phenotypic relation into an estimate of the proportion of additive genetic variance shared between trait pairs (ρ_G, genetic correlation) and an estimate of the proportion of the residual environmental variance due to shared effects of unmeasured environmental factors. (ρ_E, nongenetic correlation). Genetic correlations differing from zero indicate pleiotropy. To avoid an overestimation of genetic effects due to nongenetic factors that may be shared within each family and may be associated with the AUDIT scores and STAI state and trait scores, adjustment was done for age and squared age.

Results

As shown in Table 1, there were significant differences in alcohol-related characteristics, and state and trait anxiety scores by gender ($P < .001$). Men reported higher mean AUDIT scores and higher mean alcohol consumption compared to women, while women were more likely to report greater scores for state and trait anxiety compared to men. To our surprise, the percentage of men classified as hazardous alcohol users was 68%. Table 2 presents the associations between hazardous alcohol use and quartiles of state or trait anxiety scores. Compared to women classified into the lower three quartiles of state or trait STAI score, women categorized into the 4th quartile of state or trait anxiety scores were 15–17% more likely to be hazardous alcohol users after adjusting for age, smoking status, and educational level. In contrast, there were no significant associations between these phenotypes in men.

The intraclass correlation and heritability for the AUDTI and STAI scores are shown in Table 3. The intra-

TABLE 1

Characteristics of Subjects in the Healthy Twin Study

	Overall (*n* = 1748)	Men (*n* = 835)	Women (*n* = 913)
		Mean ± SD, n (%)	
Age (y)[a*]	41.4 ± 11.7	43.1 ± 12.6	39.8 ± 10.6
Family structure[b*]			
Monozygotic twins	656 (37.5)	278 (33.3)	378 (41.4)
Dizygotic twins	173 (9.9)	82 (9.8)	91 (10.0)
Non-twin family members	919 (52.6)	475 (56.9)	444 (48.6)
AUDIT score[a*]	8.5 ± 7.0	11.9 ± 7.3	5.4 ± 5.0
Hazardous alcohol use (AUDIT ≥ 8)[b*]	786 (48.0)	569 (68.1)	217 (23.8)
Alcohol consumption (g/week)[a*]	113.9 ± 210.3	183.4 ± 269.3	49.9 ± 98.1
State score of STAI[a*]	41.5 ± 10.2	40.2 ± 9.3	42.7 ± 10.7
Trait score of STAI[a*]	42.5 ± 9.7	40.8 ± 9.0	44.1 ± 10.0
Education (≥ graduated high school)[b]	1425 (81.8)	682 (81.8)	743 (81.8)
Current smoker[b*]	518 (29.7)	431 (51.7)	87 (9.5)

Note: AUDIT, alcohol use disorders identification test; STAI, State Trait Anxiety Inventory.
[a] *t* test or [b] χ^2-test by sex.
*$P < .05$

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TABLE 2

The Associations Between the STAI and Hazardous Alcohol Use in Subjects of the Healthy Twin Study (n = 1748)

	Odds ratio (95% C.I.)			
	Men		Women	
	Age-adjusted[a]	Fully-adjusted[b]	Age-adjusted[a]	Fully-adjusted[b]
State-STAI				
4th quartile	0.99 (0.89–1.11)	0.99 (0.90–1.10)	1.22 (1.11–1.35)	1.17 (1.06–1.29)
Lower three quartile	1	1	1	1
Trait-STAI				
4th quartile	0.95 (0.85–1.06)	0.94 (0.84–1.04)	1.22 (1.11–1.34)	1.15 (1.05–1.26)
Lower three quartile	1	1	1	1

Note: STAI, State and Trait Anxiety Inventory.
[ab] Method of generalized estimation equation including predictors ([a]age and quartiles of STAI score; [b]age, quartiles of STAI score, smoking, and education level).

class correlation coefficients for these phenotypes within MZ twin pairs were higher compared with those values within DZ twin pairs. In general, the heritability estimates for the three phenotypes were a little variable by sex: for the state score, 0.26 in men and 0.34 in women; for the trait score, 0.35 in men and 0.31 in women; for the AUDIT score, 0.32 in men and 0.37 in women. Table 4 shows cross-trait correlations between the AUDIT and the state or trait anxiety scores from the same individuals by sex. After adjusting for age and squared age, there were no significant genetic or non-genetic correlations between these phenotypes in men, while there was a significant genetic correlation between the trait score and the AUDIT score, and a significant non-genetic correlation between the state score and the AUDIT score in women. For the relationship between state and trait anxiety scores, the correlations explained by the genetic and non-genetic share were very high; thus, there was a pleiotropic relationship between the two phenotypes regardless of sex.

Discussion

Previous work has documented a positive association between anxiety and AUD in general populations (Kushner et al., 1990; 1999; 2000; Pohorecky, 1991) and in twins and families (Mullan et al., 1986; Tambs et al., 1997). This association has been interpreted as anxiety and AUD both contributing to the development of the other, and anxiety disorder being a maintaining or relapsing factor for AUD (Kushner et al., 2000). However, these studies have either been carried out among Caucasians or have not been obtained from population-based twins and their families. Therefore, it is unclear whether the relationship found in the past studies would be generalized to families of Asian ethnicity. In this study we examined the relationship among Korean twins and their families recruited from the general population using the AUDIT score and the state and trait scores of STAI.

We found that in women higher state or trait anxiety was associated with increased risk of hazardous alcohol use, while the associations were not significant in men. These findings extend those of previous studies, confirming the coexistence of anxiety and AUD (Kushner et al., 1990; 1999; 2000; Pohorecky, 1991). In addition, the similar magnitude of associations for the state and trait anxiety scores in relation with hazardous alcohol use may be explained by the high correlation between the two traits, which has been demonstrated among Caucasian

TABLE 3

Intra-Class Correlation and Heritability of the STAI and AUDIT Scores in Subjects of the Healthy Twin Study (*n* = 1748)

		Intra-class correlations (95% CI)		Heritability (SE)		Environmental effect (SE)		Variation explained by covariates[a]
		MZ twins (n = 268 pairs)	DZ twins (n = 69 pairs)	Crude	Adjusted[a]	Crude	Adjusted[a]	
State-STAI	Men	0.38 (0.27, 0.47)**	0.11 (-0.13, 0.34)	0.26 (0.08)**	0.26 (0.08)**	—	—	0.0005
	Women			0.35 (0.06)**	0.34 (0.06)**	—	—	0.006
Trait-STAI	Men	0.40 (0.29, 0.49)**	0.16 (-0.08, 0.38)	0.35 (0.08)**	0.35 (0.08)**	—	—	—
	Women			0.31 (0.11)**	0.31 (0.11)**	0.04 (0.08)	0.04 (0.08)	—
AUDIT	Men	0.57 (0.48, 0.64)**	0.34 (0.11, 0.53)**	0.32 (0.12)**	0.32 (0.12)**	0.14 (0.09)	0.13 (0.09)	0.004
	Women			0.27 (0.12)*	0.37 (0.13)**	0.14 (0.09)	0.05 (0.10)	0.06

Note: MZ, monozygotic; DZ, dizygotic; STAI, State and Trait Anxiety Inventory; AUDIT, alcohol use disorders identification test.
[a]Estimates (standard error) were assessed after adjusting for covariates (age and squared age).
*$P < .05$, **$P < .001$.

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TABLE 4

Cross-Trait Correlations Between STAI and AUDIT Scores From the Same Individuals Among Subjects of the Healthy Twin Study (n = 1748)

		Spearman correlation	ρ_G (SE)		ρ_E (SE)	
			Crude	Adjusted [a]	Crude	Adjusted [a]
State and trait scores	Men	0.81**	0.88 (0.05)**	0.88 (0.05)**	0.79 (0.03)**	0.79 (0.03)**
	Women	0.79**	0.84 (0.04)**	0.85 (0.04)**	0.78 (0.02)**	0.78 (0.02)**
State and AUDIT scores	Men	0.13**	0.11 (0.16)	0.08 (0.17)	0.16 (0.08)*	0.15 (0.08)
	Women	0.13**	0.18 (0.13)	0.17 (0.13)	0.17 (0.06)*	0.19 (0.06)*
Trait and AUDIT scores	Men	0.12**	0.08 (0.14)	0.04 (0.15)	0.15 (0.08)	0.15 (0.08)
	Women	0.13**	0.30 (0.12)*	0.30 (0.12)*	0.10 (0.06)	0.11 (0.06)

Note: STAI, State and Trait Anxiety Inventory; AUDIT, alcohol use disorders identification test; ρ_G, Correlation explained by genetic share; ρ_E, Correlations explained by non-genetic share; SE, standard error.

[a] Adjusted for age and squared age.

*$P < .05$, **$P < .001$.

populations (Spielberger, 1983). Furthermore, we found in women a significant genetic correlation between the trait anxiety score and the AUDIT score, and a significant nongenetic correlation between the state anxiety score and the AUDIT score, while in men there were no significant genetic or nongenetic correlations between these phenotypes. This study therefore indicates an evidence of pleiotropy between the trait anxiety score and AUDIT score in women. In contrast, in sex-specific correlations from the Norwegian Twin study, common genetic effects fully explained the correlation between anxiety/depression symptoms and alcohol consumption in males (r = 0.23), while the correlation in females (r = 0.18) was explained by individual environmental factors with either genetic effects or family environment (Tambs et al., 1997).

Most notably, this is the first study to our knowledge to investigate the genetic or nongenetic correlations between the AUDIT score and the state or trait anxiety scores. In this study, the heritability estimates of state and trait anxiety scores were 0.26 and 0.35 in men, and 0.34 and 0.31 in women, respectively, which were lower than those estimates (0.45 and 0.89, respectively) among bipolar extended families (Contreras, 2009). However, our finding did not provide shared environmental effects for both of state and trait anxiety scores, which differs from studies among adolescents (Lau et al., 2006; Legrand et al., 1999). In these studies, state anxiety was mostly influenced by environmental factors, particularly those from nonshared sources, with an almost negligible genetic influence, whereas trait anxiety showed moderate genetic effects and substantial nonshared environmental effects (Lau et al., 2006; Legrand et al., 1999).

The disparate findings between the studies may be explained by differences in the survey tools, the criteria used for anxiety and AUD, the source of subject sampling, and the study design. First, the sensitivity and specificity of measures used to identify anxiety and AUD between studies would vary. The positive and negative predictive values of the tools are also influenced by the prevalence of the disease in the population sampled, that is, the sampling source. Second, the diagnostic criteria for anxiety and AUD would be inconsistent, that is, some tools focus on panic disorder and alcohol abuse, while others consider generalized anxiety disorder and alcohol dependence. A review of the relevant epidemiologic, family, and field studies suggests that the various anxiety disorders have different relationships with AUD. For example, agoraphobia and social phobia appear to demonstrate a consistent and robust relationship with AUD, while simple phobia does not appear to be related to alcohol-related problems (Kushner et al., 1990). Third, clinic sampling subjects are likely to be individuals possessing a greater severity of anxiety and AUD, which may be associated with familial aggregation (Low et al., 2008). Therefore, data from clinical samples tend to show a clear association between AUD and anxiety, whereas self-reported data from general population studies have demonstrated a weak or absent relationship. Finally, in cross-sectional studies, anxiety symptoms may be related to true anxiety or secondary symptoms of alcohol-related problems. As acute alcohol withdrawal symptoms resemble some anxiety symptoms, when anxiety symptoms are surveyed during acute alcohol withdrawal, it would be difficult to differentiate true anxiety symptoms from alcohol withdrawal-related symptoms (Schuckit & Hesselbrock, 1994). Similarly, it is not possible to conclude causality of anxiety and alcohol-related problems or the persistence of the relationship using a cross-sectional study design.

Some limitations of our study need to be taken into account. Although our findings demonstrate a significant association between anxiety and AUD in a Korean population, there was a gender difference in the association. The gender difference may be related to gender difference in the validity of assessment tools. In addition, we did not assess the independence of state and trait anxiety using test–retest over time. Subjects were asked to complete the structured questionnaires that did not specifically explain about the order of answer to the questions. Therefore, it is possible that the assessment of trait anxiety may be influenced by state anxiety and that anxiety state may be

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influenced by circumstances. This interaction between state and trait anxiety and situations may lead to a low estimation of heritability (Lau et al., 2006). Future work should therefore include studies designed to evaluate gender-specific validity of the AUDIT and the STAI scores and also exclude possible interaction between state and trait anxiety. Our results are also encouraging and should be validated in other Asian populations

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