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The Genetic Correlation Between Cigarette Smoking and Alcohol Drinking Among Chinese Adult Male Twins: An Ordinal Bivariate Genetic Analysis

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Background: Though multiple policies have been implemented, the cigarette control in China is still facing a great challenge. At the same time, alcohol drinking has increasingly become a public health problem. Considering cigarette smoking and alcohol drinking often co-occur, a few studies tested the covariance of these phenotypes. However, the genetic and environmental correlation between them among Chinese population has not been determined. The main aim of this study is to fill this gap. *Methods:* From the Chinese National Twin Registry, we obtained the data on cigarette smoking and alcohol drinking behaviors. The ordinal bivariate genetic analysis was performed to fit the categorical variables. After identifying the best decomposition among the Cholesky, common, and independent pathway model, we established the most parsimonious submodel. *Results:* The correlation between current tobacco and alcohol use could be explained by Cholesky model. The shared environmental variances for both phenotypes were dropped to construct the most parsimonious submodel. Furthermore, the most parsimonious submodel showed a moderate correlation (0.32, 95%CI = 0.17 – 0.46) between the genetic components and a negligible non-shared environmental correlation. *Conclusion:* As the first bivariate genetic analysis on current tobacco smoking and current alcohol drinking in China, this study suggested a common genetic vulnerability to tobacco and alcohol use in male twins. Further studies should be carried out to track the pertinent genes that are related to the comorbidity of smoking and drinking in Chinese population. Another urgent need is to recognize the behavior-specific environmental risk factors.

■ **Keywords:** Genetic correlation, tobacco, alcohol, heritability, male, China

At present, the prevalence of cigarette smoking is considerable in China. The latest national survey showed that the overall prevalence of cigarette smoking of people aged 15 years or above in China was 24.0% (Ma et al., 2005; Yang et al., 2005). More than half of all males (50.2%) were smokers. The proportion of smokers among males was nearly 18 times that among females, which was 2.8%. Among male smokers, 98.8% still smoked, which meant that 49.6% of male in China were current smokers. According to the same survey, the overall current alcohol drinking prevalence of people aged 15 years and above in China was 21.0%, and the proportion of drinkers among males (39.6%) was more than eight times that among females (4.5%) (Ma et al., 2005).

Considering the high prevalence of cigarette smoking, cigarette control in China is facing a great challenge, despite multiple policies that have been implemented (Lv et al., 2011). At the same time, alcohol drinking in China, which is normative among adult men during social occasions, is not considered to be a problem behavior (Lessov-Schlaggar

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et al., 2006). Therefore, in scientific research, it has not received much attention. However, alcohol drinking has been a public health problem in China (Ma, Zhu et al., 2005); so, it is necessary to do further surveys to reveal the influencing factors.

A number of studies done on twins have shown that the genetic influences play an important role in explaining individual differences in current cigarette smoking and alcohol drinking. The heritability of these two phenotypes in Chinese males calculated by the univariate genetic models were 75.1% and 59.5%, respectively (Lessov-Schlaggar et al., 2006). The high heritability estimates of these two phenotypes indicated important genetic factors in the etiology of smoking and drinking.

Cigarette smoking and alcohol drinking are two kinds of addictive behaviors which often co-occur, especially in regular smokers (Kristjansson et al., 2011). The relationship between cigarette smoking and alcohol drinking has been a subject of interest for clinicians and researchers for a long time, but it was not concluded as to what extent the common genetic and environmental factors influence on tobacco and alcohol use.

In China, no study has ever estimated the genetic and environmental correlation between current smoking and alcohol drinking in genetically informative samples. To fill this gap, we analyzed a representative community-based sample of Chinese male twins to determine the genetic and environmental influences on the covariance of these two phenotypes in the present study.

There was a prevailing hypothesis in previous studies that assumed a general non-specific underlying genetic risk factor, which could increase one's liability of substance use. But instead of following the previous theory, we tried to identify the best model by comparing three different ways of decomposition (Cholesky, common pathway, and independent pathway) to the saturated model.

Materials and Methods

Study Design and Participants

The data for the analyses in the present study come from the population-based Chinese National Twin Registry (CNTR), which was established in 2001 (Gao et al., 2006). More than 6,000 twins of all age and sex have been enrolled through the local disease control network, mass media, and residence registry. Based on the registry, cohorts of 1,008 twins were established in two areas — Qingdao, Shandong province and Lishui, Zhejiang province (Li et al., 2006). By the end of 2005, the survey data, including demographic characteristic, tobacco and alcohol use, etc., were collected from this cohort (Li et al., 2006). On the grounds that almost none of the female twins were smoking cigarettes (0.2%) or drinking alcohol (1.9%) at that time, the questionnaire data of cigarette smoking and alcohol drinking from only the male twins were used.

This study was approved by the institutional review board at the Health Science Center, Peking University. Written-informed consent was obtained from every participant at the time of investigation.

Zygosity Determination

Zygosity of the CNTR was determined mainly by two steps (Gao et al., 2006; Lee et al., 2010). First, opposite sex twins and same sex twins who had different ABO blood types were classified as dizygotic (DZ) twins. Second, for the sake of determining the zygosity of same-sex twins, PCR-amplified short tandem repeat (STR) analysis was applied using an AmpF1STR Profiler PlusTM PCR kit(PE Co., USA) that comprised 10 autosomal, codominant, unlinked loci (D3S1358, vWA, D16S539, D2S1338, D8S1179, D21S11, D18S51, D19S433, TH01, FGA) and amelogenin — the gender-determining marker. Monozygotic (MZ) twins were determined when all these unlinked loci and the gender-determining marker were identical. If more than two alleles were discordant, then DZ twins were confirmed. The probability of MZ determined by identity of 10 STRs is estimated to be at least 99.9%. Since the participants in this study were all men, only the second step was actually playing a role.

Phenotypes

Questions regarding cigarette smoking and alcohol drinking were asked in an identical manner and were similarly defined. Depending on a two-category measure 'Do you smoke?', the participants who answered 'Yes, I smoke' were defined as current smokers. The same way was used when defining current drinkers (those who answered 'Yes, I drink' to the item 'Do you drink alcohol?').

Statistical Analyses

The demographic characteristics of male twins were described. Next, tetrachoric correlation coefficients for smoking and drinking in MZ and DZ group were calculated. Then, the odds ratio (OR), calculated by binary logistic regression analysis and corrected for non-independence by the use of generalized estimation equation (GEE), was used to investigate the phenotypic association between cigarette smoking and alcohol drinking. These steps were carried out with PASW Statistics, Release Version 18 (© SPSS, Inc., 2009, Chicago, IL, www.spss.com). Finally, quantitative genetic analysis was performed. As both phenotypes were dichotomized, the bivariate categorical threshold model was fitted with OpenMx (Boker et al., 2011). OpenMx is a free, full-featured, and open source program for structural equation model (SEM), and works as an integral part of R statistical software (R Development Core Team, 2010).

Structural equation model (SEM) is a kind of linear model including not only the manifest variables but also the latent variables. In classical twin genetic modeling, SEM is used to decompose the variation of phenotypes into additive genetic (A), dominance genetic (D), shared

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environment (C), and non-shared environment (E) variance components. These four factors are virtually latent variables. Genetic material passes on from parents to their offspring, which contribute to greater similarity between twin pair members. The distinction between A and D is that A presents the additive effects of genes on multiple loci but D indicates the interactions between alleles at the same locus or on different loci. MZ twins share 100% of their genetic material (additive and dominance) and DZ twins share, on average, 50% of their additive genetic material and 25% of their dominant genetic material. C also contributes to twin pair similarity. It is further assumed that environmental factors are shared to the same extent in members of MZ and DZ twin pairs, in accordance to the Equal Environment Assumption (EEA). Though EEA had been criticized for a while (Eaves et al., 2003), it was shown to hold true for tobacco and alcohol use in large twin populations (Hettema et al., 1999). Derks et al. (2006) also clarified that there was no violation of the EEA in multivariate twin studies (Derks et al., 2006). E is unique to each member of a twin and also includes measurement error. E contributes to twin's dissimilarity. D and C are confounded in a twin design, so they cannot be estimated simultaneously. If the MZ twin correlation is more than two times that of DZ twin correlation, then the ADE model should be chosen. Otherwise, the ACE model should be fitted. Multivariate models could also estimate the common genetic and environmental components of the covariance among variables.

At the beginning, a phenotypic saturated model was run. Then, three multivariate genetic models — the Cholesky, the common pathway, and the independent pathway models — were performed (Ball et al., 2011). The models were fitted to the raw data.

In Cholesky model, the first genetic factor did not only account for all the genetic variance on the first variable, but also allowed to influence the second one. The other genetic factor accounted for the remainder of genetic variance on the second variable. There were corresponding factors for shared and non-shared environmental influences. Moreover, the Cholesky model could be easily converted into correlated factor model. It was shown that the use of a Cholesky model may lead to boundary problems (a matter of degree, not of kind), but the degree to which this may concern the analysis of ordinal variable is not clarified to date (Carey, 2005). In the common pathway model, one common latent variable, which loaded on to both variables, was assumed. The common latent variable was constrained to have a variance of 1, and had its own genetic, shared, and non-shared environmental factors. While there were also specific genetic, shared, and non-shared environmental factors to each of the two variables, in independent pathway model, three common factors A, C, and E could independently influence both phenotypes; at the same time, specific A, C, and E were allowed to influence on every variable.

TABLE 1
Demographic Characteristic of the Participants

Demographic characteristics	Qingdao (%)	Lishui (%)	*P* value
n (individuals)	388 (43.1)	512 (56.9)	
Zygosity			
MZ	292 (75.3)	394 (77.0)	.554
DZ	96 (24.7)	118 (23.0)	
Age (years)	39.1 ± 10.4	38.8 ± 11.1	.744
Currently working	363 (93.6)	472 (92.2)	.432
Current cigarette smoking	227 (58.5)	298 (58.2)	.927
Current alcohol drinking	129 (33.2)	192 (37.5)	.187

These three genetic models were each nested within the saturated model, and it was plausible to assess the fit of them by comparing them to the saturated model on the basis of Chi-square test (the difference in -2 times log likelihood (Δ-2ll) approaches a Chi-square distribution). In addition, Akaike Information Criterion (AIC, AIC = Chi-square – 2 degree of freedom) was used to compare the three models (Akaike, 1987). The model, which had the lowest AIC value, was better than the other two. After this, some components among A, C, and E were dropped from the best fitting model so as to simplify the model. As outlined above, other than Chi-square and *P* values, AIC value would be used to select the most parsimonious submodel. Estimates of heritability and relevant correlation coefficient were derived from the most economical submodel and presented with 95% confidence intervals (CIs).

Results

Demographic Characteristics

There were 450 male twins (i.e., 900 individuals) in this study. As Table 1 shows, 43.1% of them were enrolled from Qingdao, and 56.9% from Lishui. The zygosity distribution between Qingdao and Lishui twins in this study was similar ($P = .554$). The average age was the late 30s, and there was no significant difference between Qingdao and Lishui twins ($P = .744$). More than 90% male twins were currently working, and there was no significant difference between two regions ($P = .432$). Both regions had reports of more than 58.0% of the participants being current smokers, and about one-third participants being current alcohol drinkers. The distributions of current cigarette smoking and current alcohol drinking in two regions were similar as both *P* values were more than .05.

Twin Correlations

Table 2 displays the tetrachoric correlation coefficients (within-twin cross-trait, cross-twin within-trait, and cross-twin cross-trait) for smoking and drinking by zygosity. All MZ twin correlations were less than twice those of DZ correlations, so ACE model was fitted in preference to ADE model.

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TABLE 2

Tetrachoric Correlation Coefficients with Standard Error for Smoking and Drinking by Zygosity

	cross-twin within-trait			
	smoking	drinking	within-twin cross-trait	cross-twin cross-trait
MZ	0.6697 (0.0565)*	0.7827 (0.0453)*	0.2858 (0.0590)*	0.2050 (0.0607)*
DZ	0.5430 (0.1203)*	0.5405 (0.1218)*	0.2045 (0.1065)	0.1736 (0.1074)

Note: *$P < .05$.

TABLE 3

Twins Genetic Model Fit Statistics

	Model fit statistics			Fit statistics (compared to phenotypic saturated model)			
Model	–2 ll	AIC	df	Δ–2 ll	ΔAIC	Δdf	*P* value
Saturated	2154.92	−1405.08	1780	–	–	–	–
Cholesky	**2161.59**	**−1412.41**	**1787**	**6.66**	**−7.34**	**7**	**.46**
Common pathway	2161.60	−1410.40	1786	6.68	−5.32	6	.35
Independent pathway	2161.59	−1406.41	1784	6.66	−1.34	4	.15

Note: The best fitting model is in bold. –2ll = –2 Log Likelihood. AIC = Akaike Information Criterion. df = degree of freedom.

The OR of reporting current alcohol drinking, if reporting current cigarette smoking, was 2.04 (95% CI = 1.47–2.83).

Model Fitting

Table 2 presents the model fit statistics. Compared to the phenotypic saturated model, all of the Cholesky, common pathway, and independent pathway models fitted well (Δ-2 ll = 6.66, 6.68, and 6.66, respectively. $P = .46$, .35, and .15, respectively). Thus the AIC values were used to identify the best model among these three models. The Cholesky model was selected as the best one on the basis of having the lowest AIC value (AIC = –1412.41, ΔAIC = –7.34), which also had the biggest degrees of freedom (1,787). Therefore, the correlated variance between cigarette smoking and alcohol drinking could be best explained by Cholesky decomposition.

In the principle of thriftiness, the comparison between Cholesky ACE model and its nested submodel was performed. The fit statistics were showed in Table 3. Cholesky˙noc denoted the submodel, which dropped C of cigarette smoking and alcohol drinking simultaneously. The submodel Cholesky˙noa and Cholesky˙noac dropped A and A & C of both variables, respectively. After dropping C or A, the model fit was not significantly degraded ($P = .28$ and .11, respectively). But it was not suitable to drop all of A and C components concurrently ($P < .01$).

Furthermore, from the Cholesky˙noc model, we tried to drop A of the first variable (i.e., Cholesky˙noa1c), then the second variable (i.e., Cholesky˙noa2c), and next the correlated genetic components between two variables (i.e., Cholesky˙noa21c), but none of them keep a good fit. We also attempted to drop corresponding C components from the Cholesky˙noa model, yet bad fit results appeared.

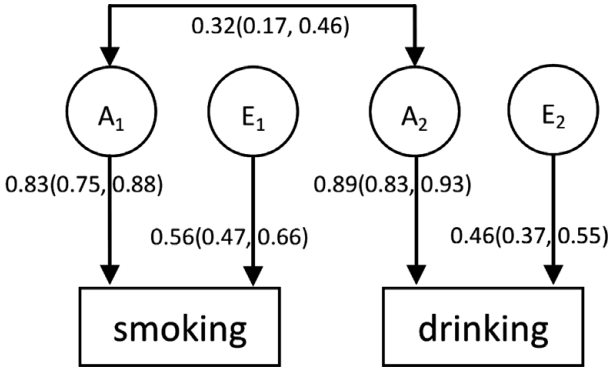

FIGURE 1

Best-fitting correlated factor model (smoking = current cigarette smoking, drinking = current alcohol drinking).

In order to find out whether there was a significant correlated E component, we ran the submodel of Cholesky˙noce21 and Cholesky˙noae21, neither of which were significantly different from the Cholesky model ($P = .17$ and .07, respectively). This meant that the correlated component of non-shared environmental factors could be deleted. At last, the Cholesky˙noce21 was chosen as it had lower AIC value (–1,414.06).

Figure 1 displayed the standard path coefficients of the best fitting submodel of Cholesky ACE model, which was converted into correlated factor model. The heritability was estimated to be 68.3% (95% CI = 56.8%–77.7%) for current cigarette smoking, and 79.0% (95% CI = 69.3%–86.3%) for current alcohol drinking. The genetic correlation between A_1 and A_2 was estimated to be 0.32 (95% CI = 0.17–0.46). Because it was significantly different from zero at the 0.05 level, it supported the genetic overlap in the etiology of these

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TABLE 4
Cholesky ACE Model and Submodels

	Model fit statistics			Fit statistics (compared to Cholesky model)			
Model	–2 ll	AIC	df	Δ–2 ll	ΔAIC	Δdf	*P* value
Cholesky	2161.59	−1412.41	1787	–	–	–	–
Cholesky_noc	2165.38	−1414.62	1790	3.79	−2.21	3	.28
Cholesky_noa	2167.73	−1412.27	1790	6.14	0.14	3	.11
Cholesky_noac	2370.22	−1215.78	1793	208.64	196.64	6	<.01
Cholesky_noa1c	2255.69	−1328.31	1792	94.10	84.10	5	<.01
Cholesky_noa2c	2235.16	−1346.84	1791	73.57	65.57	4	<.01
Cholesky_noa21c	2175.97	−1406.03	1791	14.38	6.38	4	.01
Cholesky_noce21	**2167.94**	**−1414.06**	**1791**	**6.35**	**−1.65**	**4**	**.17**
Cholesky_noac1	2260.25	−1323.75	1792	98.66	88.66	5	<.01
Cholesky_noac2	2235.13	−1346.87	1791	73.54	65.54	4	<.01
Cholesky_noac21	2179.42	−1402.58	1791	17.84	9.84	4	<.01
Cholesky_noae21	2170.36	−1411.64	1791	8.77	0.77	4	.07

Note: The most parsimonious submodel is in bold. –2ll = –2 Log Likelihood. AIC = Akaike Information Criterion. df = degree of freedom.

two behaviors. The non-shared environmental influences, which included measurement error, accounted for 31.7% (95% CI = 22.3%–43.2%) and 21.0% (95% CI = 13.7%–30.7%) of the variance for behaviors of tobacco and alcohol use, respectively. The correlation between E_1 and E_2 was not observed.

Discussion

In this study, we examined the common genetic and environmental effects of tobacco and alcohol use by structural equation model in a sample of population-based Chinese male twins. To our knowledge, this was the first study that reported the genetic correlations between current smoking and current drinking in China. These measures were categorically defined, so the bivariate threshold genetic model was used (Gjerde et al., 2011).

Undoubtedly, cigarette smoking was obviously influenced by genetic factors and not significantly by shared environmental effects, which was consistent with that reported in adult twins of Western origin (Madden et al., 1999; Madden et al., 2004; True et al., 1997). In terms of current alcohol drinking, the heritability calculated in this study (79.0%) was even higher than that of previous studies, either in Chinese or Western populations (Lessov-Schlaggar et al., 2006; Walters, 2002).

The use of the multivariate ACE model is not uniform in the area of behavior genetics. In the past, researchers were prone to directly choose one of them (e.g., Cholesky model), or apply and compare two of them (e.g., Common pathway model and Independent pathway model) in their studies (Kendler et al., 2007; Swan et al., 1996; True et al., 1999). In fact, in selecting the best way of decomposition, diverse models should be compared to the saturated model at first. Through comparison, we found that the Cholesky model was the best fit for the present data.

Then we simplified the Cholesky model in the principle of parsimony. Although both the Cholesky˙noce21 and Cholesky˙noae21 were acceptable models, because they both were not significantly different from the Cholesky model ($P > .05$ in Table 4), we chose the former one because it had smaller AIC value. Although the genetic variance could be over-estimated, we thought it was better than the Cholesky˙noae21 model. After all, some of the common environment factors (such as the selection of smoking or drinking friends) were partly contributed by genes. All of the following three points reflected by the most parsimonious submodel were not exactly the same as previous investigations using European or American populations.

First, there was significant correlation (0.32, 95%CI = 0.17 – 0.46) between additive genetic components of cigarette smoking and alcohol drinking, which meant the behaviors had overlapping genetic factors. Therefore, for tobacco and alcohol use in China, the common vulnerability included genetic factor. But when comparing to Western studies, this correlation was lower. The genetic correlation between tobacco and alcohol use in white male World War II US veteran twins (52–66 years old) presented by Swan et al. (1996) was 0.47 (Swan et al., 1996). While using another US military male twins who served on duty during the Vietnam era (VET Registry), True et al. (1999) found an even bigger genetic correlation of 0.68 (True et al., 1999). In spite of that, the use of one substance still could be served as genetic cue for the use of the other in the Chinese population.

The evidence has been converging that the comorbidity of tobacco and alcohol use originated at least partially from genetic risk, not only for adults but also for adolescents as well. Certain genes, such as CHRNA5, CHRNA3, and CHRNB4, have been found to be related to the co-occurrence of these behaviors, just not in Chinese population (Chen et al., 2009; Ehringer et al., 2007; Schlaepfer et al., 2008a; Wang et al., 2009). Candidate genes should be tested to determine their effects on smoking and drinking

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behaviors of Chinese people. Furthermore, if the underlying molecular mechanisms of specific genetic variations associated with these behaviors were characterized, then the approaches of tobacco and alcohol control could be improved (Schlaepfer et al., 2008b).

Second, there is a lack of shared environmental influence (early family environment) according to the best fitting submodel. The existence of shared environmental components and the correlation between them produced the most complex situation in the area of substance use. On the first hand, results from adolescent twins presented vital shared environmental correlation. For example, in their study using an adolescent sample, Young et al. (2006) presented significant but modest correlation (0.22) in shared environmental influences, as well as genetic influences (0.15), in repeated alcohol and cigarette use (Young et al., 2006). Han et al. (1999) and Koopmans et al. (1997) also established evidence of a common vulnerability factor that was explained by shared environmental factors in samples of teenagers (Han et al., 1999; Koopmans et al., 1997). This was logical because adolescent twins had more shared surroundings from their parents or near their neighborhood. On the other hand, for adults, even family environment influenced greatly on the initiation of substance use behaviors while they were adolescents, it was still unlikely to put effect on the status of smoking and drinking by then. At least, we did not find that shared environmental factors were significant for either of these conduct in the present study, and thus there was naturally no common shared environmental factor which contributed to comorbidity between tobacco and alcohol use. It was also confirmed by some other researches (Haberstick et al., 2007; Hettema et al., 1999; Hopfer et al., 2001; Kendler et al., 2007; Sartor et al., 2009; Unger et al., 2010) but not all.

Third, this study showed a negligible level of correlation within the non-shared environmental variance, which was not equal to corresponding studies conducted in twins of Western origin. For example, non-shared environmental correlation was modest and significant (0.23) among middle-aged military male twins from VET Registry (True et al., 1999). The disparity was possibly attributable to differences in the nature of populations and variability of cultures. Therefore, in casting light on the environmental causes of cultural differences in substance use behaviors, a combination of comprehensive environmental factors in future research would be valid. For example, it is inferred that one partner's cigarette or alcohol involvement may affect the other partner's behavior of substance use by 'marital contagion' (Agrawal et al., 2006). However, frankly speaking, it is still not conclusive whether similarity contributes to assortative mating (i.e., cigarette smokers marry other cigarette smokers) or non-random mating modifies population variation for substance use. The Chinese National Twin Registry is initiating a new round of investigation, which will integrate the extensive and concrete environmental factors into the research and go into the analysis of gene-environment interaction.

This manuscript used current cigarette smoking and alcohol drinking as the studied phenotypes, which helped to reduce recall bias. However, several limitations of this study should be kept in mind. First, genetic analysis was only performed in a sample of male twins, so the result cannot be generalized to females, and the sample may be more representative of east area dwellers. Additionally, the expression of genetic and environmental influences on substance use may change substantially during the developmental period or with education level (Hettema et al., 1999; Johnson et al., 2011). For the purpose of elucidating the effects of changing genetic and environmental influences on substance use behaviors, age- or education-based stratification or longitudinal analysis should be implemented.

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