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RESEARCH ARTICLE

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RETN gene polymorphisms interact with alcohol dependence in association with depression

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Abstract

Background: Previous studies suggest that alcohol dependence is associated with increased risk of depression. The occurrence of depressive symptoms is related to polymorphisms in various genetic regions. This study aimed to investigate the interaction of *RETN* gene polymorphisms (rs1477341, rs3745368) with alcohol dependence on depressive symptoms in adult male during acute alcohol withdrawal.

Methods: A total of 429 male adults were recruited in this study. Alcohol dependence was assessed using the Michigan alcoholism screening test (MAST). Depression was assessed using the 20-item self-rating depression scale (SDS). Hierarchical regression analysis was used to evaluate the interaction between genes and alcohol dependence on depression. Region of significance (ROS) test was used to explain the interaction effect. The strong and weak forms of the differential susceptibility and diathesis models were used to determine which fits the data better.

Results: Our results showed that MAST scores were significantly positively associated with SDS scores ($r = 0.23$, $p < 0.01$) in alcohol-dependent patients during alcohol withdrawal. The interaction between genotype and alcohol dependence was significant ($\beta = -0.14$, $p < 0.05$) in a strong diathesis-stress model. Susceptibility for depression symptoms was associated with alcohol dependence in *RETN* rs1477341 *A* carriers. Specifically, those that showed more alcohol dependence and the *A* allele of *RETN*

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rs1477341 exhibited more depression symptoms. However, *RETN* rs3745368 had no significant interaction with alcohol dependence.

Conclusions: The *A* allele of *RETN* rs1477341 may correlate with susceptibility to depression symptoms in alcohol-dependent individuals during acute alcohol withdrawal.

KEYWORDS
alcohol dependence, depression, Michigan alcoholism screening test, *RETN* gene polymorphisms, self-rating depression scale

1 | INTRODUCTION

Alcohol dependence is one of the most prevalent mental disorders worldwide associating with significant morbidity and mortality.[1] Epidemiological studies found that the 12-month prevalence of alcohol dependence was 13.9% and the lifetime prevalence was 29.1%.[2] Furthermore, alcohol dependence is associated with many psychiatric comorbidities including depression.[3,4] Several studies have identified that the co-existence of alcohol dependence and depression could be a risk factor for morbidity and mortality including death from suicide.[5,6] The prevalence of depression has been reported to be higher in people with alcohol dependence than in the general population, especially during acute alcohol withdrawal.[7,8] During acute alcohol withdrawal, patients may suddenly stop or reduce alcohol intake, and this may trigger a stress response in the brain that can lead to the increase of depressive symptoms.[9] However, not all alcohol-dependent patients have depressive symptoms. One research report indicated that most patients entering alcohol treatment centers would meet the criteria for major depression, but the symptoms of 80% of patients resolve within 2 weeks through abstinence alone.[10] Due to the symptoms of depression are associated with alcohol dependence and may have dire effects during withdrawal, and factors that affect individual susceptibility to depression like genetic variation and environment need to be further elucidated.

To date, several studies on depression have confirmed the association of various genetic polymorphisms in the dopamine system, including monoamine oxidase-A (MAOA), catechol-*O*-methyl transferase (COMT), and the dopamine transporter (DAT1).[11,12] Resistin, a cytokine produced mainly by fat cells, belongs to the cysteine-rich C-terminal domain proteins and is encoded by the *RETN* gene. *RETN* has been proposed as an emerging biomarker of depression.[13] With further discoveries surrounding adipokines, an increasing number of studies have shown that Resistin is associated with depressive symptoms, especially in major depressive disorder. Clinical studies have shown that Resistin has a potential therapeutic effect on depression.[14] Studies have reported high levels of Resistin in depressive patients could be normalized by treatment.[15] Additionally, growing evidence suggests that Resistin is closely related to alcohol dependence. Specifically, chronic alcohol use may be affected by altered levels of Resistin.[16] Moreover, studies in rodents have shown that chronic ethanol consumption increased Resistin in sera.[17] Clinical studies yielded similar results and 7 days of abstinence did not normalize Resistin levels in sera.[18]

Although an increasing number of findings have demonstrated the crucial roles of Resistin in depression and alcohol dependence separately, few studies have examined the gene × environment (G × E) effect of Resistin or the relations between the genetic variation of *RETN* and susceptibility to depression. Resistin regulates both food- and alcohol-seeking behavior, and the latter is observed in patients with alcoholism.[16] Previous studies have shown that circulating resistin levels correlate with *RETN* 3 "region snp" (rs1477341). Moreover, rs1477341 was significantly correlated with an increased TG level and a decreased TC/HDL-C level.[19] In addition, it has been reported in the literature that the presence of the *RETN* rs3745368 *A* allele was associated with an increase in resistin level.[20]

Hence, we conducted this study to assess whether *RETN* gene polymorphisms are related to depression susceptibility among individuals undergoing acute alcohol withdrawal (environment). To be noted, most of the existing studies on G × E interactions have been conducted under the framework of the diathesis-stress and differential susceptibility models.[11,21] The diathesis-stress model is relative to a "risk allele", while the differential susceptibility model is relative to a "plasticity allele". Specifically, individuals with the "risk allele" may suffer from adverse environmental experience and will be worse than others. On the contrary, individuals carrying "plastic alleles" not only suffer from adverse environments, but also benefit from supportive environments.[22]

The present study was designed to examine the interaction between two SNPs of *RETN* with alcohol dependence on depressive symptoms in male adults during acute alcohol withdrawal. In addition, we attempted to explore the nature of these polymorphisms × alcohol withdrawal by testing two competing hypotheses: diathesis-stress hypothesis and differential susceptibility hypothesis.

2 | MATERIALS AND METHODS

2.1 | Participants

The sample size was calculated with G Power (3.1.9.2), according to the previous Gene × Environment studies where the differences of slope between different gene subgroups ranged from approximately 0.05–0.20.[23,24] Therefore, to conduct a linear regression

with Δslope of 0.05, α value of 0.05 (two-tailed), power of 0.95, the estimated sample size was 210 participants; that is, the sample size required for the study was 210 participants.

In the current study, participants consisted of 429 male adults, recruited from several psychiatric hospitals in Northern China. They were aged from 20 to 67 years (M_{age} = 44.11, SD = 9.42), and were Chinese Han ethnicity. The inclusion criteria for the patients included a diagnosis of alcohol dependence according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria and a literate and cognitive capacity to comprehend the tests and instructions.

The exclusion criteria were as follows: (1) history of drug abuse or dependence, with the exception of nicotine; (2) presence of serious cardiovascular diseases, or liver or kidney disease; (3) dementia or history of serious neuropsychic diseases illness; (4) lacking a clear understanding of informed consent.

This study was approved by the Institutional Review Board of the Inner Mongolian Medical University. All participants read and signed a written informed consent. Then participants were requested to complete a series of questionnaires in a quiet ward and to provide their blood samples for DNA extraction.

2.2 | Measurements

2.2.1 | Alcohol dependence

The Michigan alcoholism screening test (MAST), a self-report questionnaire, was developed by Selzer[25] to screen for alcohol dependence. The MAST covers several dimensions that can be affected by alcohol consumption, including but not limited to health status, family problems, and interpersonal relationships. The test consists of 25 items, with "yes" or "no" response options. For example, "have you ever lost friends because of your drinking?" A higher score of total MAST indicates more behaviors associated with alcohol dependence.

2.2.2 | Depression

To assess the depression levels of participants, a self-rating depression scale (SDS) of 20 items was used. The SDS was created by Zung[26] as a self-report questionnaire. The participants were required to indicate how often he or she has experienced each symptom on a four-point scale (1 = "rarely or none of the time" to 4 = "most or all of the time"). Example items include "I have trouble sleeping at night." A higher score indicates more depression symptoms. The SDS has acceptable internal consistency, with a split-half reliability of 0.73.[27]

2.3 | Environment

Participants were hospitalized for alcohol dependence. The patients' access to alcohol was limited and they were therefore actively withdrawing.

2.4 | Genotyping

A salting-out method was used to extract genomic DNA with 5-mL peripheral blood sample. The primer sequences for the qRT-PCR analysis of rs3745368 and rs1477341 were ordered, and genomic DNAs were genotyped by using TaqMan SNP Genotyping Assays (C_32391819_10 and C_8351534_10; Thermo Fisher Scientific) according to the manufacturer's protocol.

2.5 | Statistical analysis

All analyses were performed using R 4.0.2 and SPSS 22.0. The Hardy–Weinberg equilibrium for genotype distributions of *RETN* rs3745368 and *RETN* rs1477341 were tested using the chi-square (χ^2) test for goodness of fit. Pearson's correlation and Spearman's correlation were conducted to examine the associations among genetic polymorphisms, age, educational years, alcohol dependence, and depression.

In accordance with the purpose of this study, traditional linear regression was conducted to evaluate the effects of gene, alcohol dependence severity during withdrawal, and the interaction of gene and alcohol dependence severity during withdrawal on depression. To screen for multicollinearity between independent variables and their interactions in the regression model, the orthogonalized method with standard regression procedures was used. Region of significance (ROS) analysis was used to test the interaction patterns of gene and alcohol dependence severity during withdrawal. This approach provides the lower and higher bound, where ±2 SD is recommended for a significant association between gene and depression.

Re-parameterized regression, a newly developed approach, was fitted to test the nature of G×E interaction.[28]

$$Y = \begin{cases} \text{Group: } D=0 & B_0 + B_1(X-C) + B_3X_2 + B_4X_3 + E \\ \text{Group: } D=1 & B_0 + B_2(X-C) + B_3X_2 + B_4X_3 + E \end{cases}$$

Here, Y is the dependent variable for depression, X is alcohol dependence severity, X_2 is the control variable: age, X_3 is the control variable: educational years, group is allele group, D=0 represents the carries of non-risk/plasticity alleles, D=1 represents the carries of risk/plasticity alleles. B_0 is the intercept, B_1 is the slope of alcohol dependence severity for non-risk/non-plasticity alleles, B_2 is the slope for alcohol dependence severity for risk/plasticity alleles, and C is the crossover point where the slopes of different groups cross. Importantly, this crossover point is a parameter in re-parameterized regression model. So, the confidence interval (CI) for C can be calculated, giving more information on the likely range for the population value of this key parameter. In addition, the diathesis-stress model and differential susceptibility model can be further subdivided into "strong" and "weak" versions. Strong versions assume that "non-risk/non-plasticity allele" carriers are unsusceptible to environment. Weak versions assume that these individuals are to a lesser extent susceptible to environments

than "risk/plasticity alleles" carriers. These models are nested within each other, So we used an *F* test to compare models if one model explains more or less variance than another one. We also used the Akaike information criterion (AIC) and Bayesian information criterion (BIC) to evaluate the model fit. This approach is especially useful for evaluating non-nested models, which cannot be compared using statistical tests.

3 | RESULTS

3.1 | Descriptive statistics

For *RETN* rs1477341, the genotype frequencies were AA: 29.37%, AT: 49.18%, TT: 21.45%, and for *RETN* rs3745368 were AA: 1.40%, AG: 25.64%, GG: 72.96%. The two SNPs were all in compliance with the Hardy–Weinberg equilibrium (*RETN* rs1477341: $\chi^2=0.04$, $p>0.05$; *RETN* rs3745368: $\chi^2=1.12$, $p>0.05$) (see Table 1). Furthermore, no significant differences in alcohol dependence severity between the genotype distributions of the two SNPs were observed. Similarly, no differences were found in depressive symptoms between genotypes (see Table 2).

Means, standard deviations, and correlation of the variables for the analysis sample are shown in Table 3. MAST scores were positively correlated with SDS scores ($r=0.23$, $p<0.01$), while the educational years were negatively correlated with MAST scores ($r=-0.19$, $p<0.01$). In addition, there were no significant associations between genetic indexes and all the other variables, including MAST scores ($p>0.05$).

3.2 | Interactions between *RETN* genotyping and alcohol dependence on depression

As shown in Table 4, we conducted a hierarchical regression analysis to predict depression from alcohol dependence for different allelic groups. There was a main effect of alcohol dependence on SDS scores ($\beta=0.24$, $p<0.05$), and greater alcohol dependence severity was associated with greater levels of depression. However, no significant main effect of *RETN* genotyping (rs1477341, rs3745368) was found ($\beta=-0.03$ to 0.08, $p>0.05$).

Regarding the *RETN* rs1477341 polymorphism, the interaction between genotype and alcohol dependence severity on depressive symptoms was significant ($\beta=-0.14$, $p<0.05$). Furthermore, the Region of significance analysis was conducted to interpret the interaction effect. As shown in Figure 1, the slopes for alcohol dependence on depression were as follows: *A* allele group (AA homozygote group and AT heterozygote group), $\beta=0.24$, $t=7.59$, $p<0.05$; TT homozygote group, $\beta=0.10$, $t=2.13$, $p<0.05$. The 95% CI of the crossover point *C* ranged from 0.12 to 1.35. The slope for *A* allele was 0.24 ($t=7.59$, $p<0.05$). The slope for TT homozygote was 0.10 ($t=2.13$, $p<0.05$). That is, individuals with the *A* allele would experience more depressive symptoms than TT homozygote individuals when alcohol dependence is severe.

In reference to the *RETN* rs3745368 polymorphism, no significant interaction effect of the genotyping and alcohol-dependence severity was found ($\beta=-0.6$, $p>0.05$).

TABLE 1 Hardy–Weinberg equilibrium *RETN* rs1477341 and *RETN* rs3745368.

Genotype	Number of people	Percentage
RETN rs1477341		
AA	126	29.37
AT	211	49.18
TT	92	21.45
	$\chi^2=0.04$	$p=0.83$
RETN rs3745368		
AA	6	1.40
AG	110	25.64
GG	313	72.96
	$\chi^2=1.12$	$p=0.29$

3.3 | Internal replication analyses

Finally, we further contrast strong and weak forms of the differential-susceptibility and diathesis-stress models to determine which provided the best fit to the data. Results involving rs1477341 × alcohol withdrawal interactions showed that the strong diathesis-stress model with $B_1=0$ explained a significant amount of variance in depression ($R^2=0.07$, $p<0.001$), in which the slope for alcohol dependence in *A* allele group was significant ($B_2=0.25$, SE = 0.04, $p<0.01$). Although the weak diathesis-stress model had one more parameter than the strong model, it did not explain more variance ($\Delta R^2=0.00$, $p>0.05$). Furthermore, the strong diathesis-stress model could explain the same variance by reducing one parameter than the strong differential susceptibility model ($\Delta R^2=0.01$, $p>0.05$), and have smaller AIC and BIC values by comparing with the weak differential susceptibility model. Results described in Table 5 indicate that, upon considering both R2 and AIC and BIC criteria, the best fitting model proved to be the strong diathesis-stress (i.e. model C). Specifically, the *RETN* rs1477341 polymorphism interacted with alcohol withdrawal in its association with depression. These results indicated that *A* allele carriers exhibit more severe depressive symptoms when alcohol dependence is severe compared to TT homozygous carriers, providing an initial indication of rs1477341 × alcohol dependence interactions.

4 | DISCUSSION

This study evaluated the interaction between *RETN* polymorphism (rs1477341, rs3745368) and alcohol dependence severity on depression in male patients during acute alcohol withdrawal (environment). The nature of G × E was explored by testing two competing models: diathesis-stress and differential susceptibility. We found

TABLE 2 Independent sample test *RETN* rs1477341 and *RETN* rs3745368.

	Age	Educational years	Alcohol dependence	Depression
RETN rs1477341				
A	44.51 (9.16)	10.64 (2.90)	9.31 (5.38)	56.69 (11.55)
TT	42.67 (10.24)	10.98 (2.79)	9.38 (5.39)	54.52 (10.22)
t	1.66	−1.01	−0.10	1.64
p	0.10	0.31	0.92	0.10
RETN rs3745368				
A	43.66 (9.35)	10.66 (2.92)	9.02 (5.18)	55.54 (11.24)
GG	44.28 (9.46)	10.73 (2.86)	9.44 (5.45)	56.48 (11.34)
t	−0.60	−0.25	−0.73	−0.77
p	0.55	0.81	0.47	0.45

TABLE 3 Descriptive statistics and correlations among study variables.

	rs1477341	rs3745368	Age	Educational years	Alcohol dependence	Depression
rs1477341	1					
rs3745368	−0.26***	1				
Age	−0.08	0.03	1			
Educational years	0.04	0.01	−0.40***	1		
Alcohol dependence	−0.07	0.03	0.18***	−0.19***	1	
Depression	−0.09	0.05	0.01	−0.01	0.23***	1
M	—	—	44.11	10.71	9.33	56.23
SD	—	—	9.42	2.87	5.37	11.31

Note: $^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$.

TABLE 4 Interaction between *RETN* genotyping (rs1477341, rs3745368) and alcohol dependence on depression.

		Depression					
	Variables	ΔR^2	*B* (SE)	*β*	*t*	*p*	95% CI
Step 1	Age	0.001	−0.001 (0.01)	−0.002	−0.04	0.97	−0.01, 0.01
	Educational years		0.001 (0.02)	0.01	0.21	0.83	−0.03, 0.04
Step 2	Alcohol dependence	0.06	0.24 (0.05)	0.24	5.00	<0.001***	0.15, 0.34
	rs1477341		0.21 (0.12)	0.08	1.78	0.08	−0.02, 0.43
	rs3745368		−0.07 (0.11)	−0.03	−0.62	0.54	−0.27, 0.14
Step 3	Alcohol dependence × rs1477341	0.02	−0.30 (0.11)	−0.14	−2.63	0.01*	−0.52, −0.08
	Alcohol dependence × rs3745368	<0.001	−0.07 (0.11)	−0.06	−0.60	0.55	−0.28, 0.15

Note: Depression is measured by SDS, alcohol dependence is measured by MAST.

Abbreviations: CI, confidence interval; MAST, Michigan alcoholism screening test; SDS, self-rating depression scale; SE, standard error.

$^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$.

that the severity of alcohol dependence increased the risk of depression symptoms. The polymorphisms of *RETN* rs1477341 correlate with susceptibility for depression symptoms of male adults dependent on alcohol during withdrawal and is consistent with the strong diathesis-stress. Susceptibility for depression symptoms was associated with alcohol dependence in *RETN* rs1477341 *A* carriers but not in TT homozygous adults. Specifically, *A* allele of *RETN* rs1477341 exhibited more depression symptoms when exposed to severe alcohol dependence symptoms during withdrawal. In addition, we attempted a comparison of *T* allele carriers with AA pure heterozygotes and observed no interaction between rs1477341 and alcohol dependence for depressive symptoms using this genotypic classification (see Table A1 in Appendix A).

Consistent with previous studies, the severity of alcohol dependence increased the risk of depression symptoms, and alcohol dependence has played an important role in the etiology of depression

symptoms.[8] Although it is not reflected in the results of this study, alcohol abuse in patients with depression cannot be ignored.[29] There is evidence of neurophysiological and metabolic links between alcohol exposure and depression.[30–32]

Our results indicate that there is no direct correlation between the two *RETN* SNPs (*RETN* rs1477341, *RETN* rs3745368) and alcohol dependence severity. Interestingly, the interaction between the *RETN* rs1477341 polymorphism and alcohol dependence was significant, and the best-fit model is strong diathesis-stress. This indicates that people with the *A* allele react differently to depression when experiencing more or less severe symptoms of alcohol dependence during acute alcohol withdrawal. This also suggests that people with the *A* allele are more prone to depressive symptoms when alcohol dependence is severe, whereas those homozygous for TT are unaffected by the severity of alcohol dependence. However, with regard to *RETN* rs3745368, the interaction between genotype and alcohol dependence was not significant.

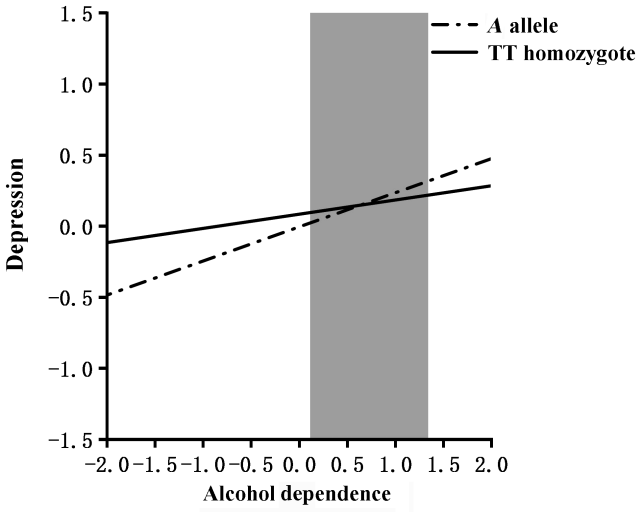

FIGURE 1 The region of significance (ROS) test on depression from alcohol dependence in *RETN* rs1477341 allelic groups. Grey shaded area represents 95% CI of the cross over point *C* of the interaction on the alcohol dependence axis. 95% CI of *C* ranged from 0.12 to 1.35. Simple slope at *A* allele = 0.24, $t = 7.59$, $p < 0.05$, Simple slope at TT homozygote = 0.10, $t = 2.13$, $p < 0.05$.

Previous literature shows that *RETN* rs1477341 and rs3745368 polymorphisms can significantly modulate plasma Resistin concentrations.[33,34] Our study has identified a role for *RETN* rs1477341 in depressive symptoms. Previous studies support that the level of Resistin is positively correlated with depressive symptoms.[35] Moreover, serum Resistin levels correlated specifically with atypical symptoms of major depressive disorder.[36] However, Pan and colleagues (2008) reported no association between self-reported depressive symptoms and the level of Resistin. Resistin has been reported to inhibit dopamine and noradrenaline release in the hypothalamus.[37] Thus, through its contribution to decreased intrasynaptic monoamine levels, it could predispose individuals to depressive symptoms. Furthermore, Volkow and colleagues proposed that cravings for alcohol and food involve similar neural pathways.[38] As an appetitive regulating hormone, Resistin is also associated with alcohol craving in alcohol-dependent patients.[16,18] In addition, it is worth mentioning that patients with depression and alcohol use disorders often have elevated inflammatory markers.[39] It is reported that Resistin is related to the activation of the inflammatory process.[40] More research is needed to determine whether Resistin plays a role in the inflammatory mechanism of depression.

It is important to consider the limitations of this study. First, perhaps the most important limitation is that we were unable to obtain the external replication evidence. Additionally, for studying G×E interactions, our sample size is relatively small. Therefore, although

TABLE 5 Results for re-parameterized regression model for depression.

	Differential susceptibility		Diathesis-stress	
Parameter	Strong:model A	Weak:model B	Strong:model C	Weak:model D
B_0	0.08 (0.37)	0.08 (0.38)	0.20 (0.36)	0.27 (0.37)
B_1	—	0.01 (0.10)	—	0.09 (0.07)
C	0.66 (0.39)	0.67 (0.46)	1.48 (—)	1.48 (—)
95% CI of *C*	−0.10, 1.42	−0.23, 1.57	—	—
B_2	0.30 (0.05)***	0.30 (0.05)***	0.25 (0.04)***	0.28 (0.05)***
B_3	0.01 (0.01)	0.01 (0.01)	0.01 (0.01)	0.01 (0.01)
B_4	−0.01 (0.02)	−0.01 (0.02)	−0.01 (0.02)	−0.01 (0.02)
R^2	0.08	0.08	0.07	0.07
F (df)	8.82*** (4424)	8.82*** (5423)	10.62*** (3425)	8.44*** (4424)
F vs. *C* (df)	3.25	1.62	—	1.84
F vs. *D* (df)	—	1.04	1.84	—
AIC	1194.16	1196.15	1195.43	1195.57
BIC	1218.52	1224.58	121.74	1219.94

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

the pattern of our results in this study was generally consistent with the previous evidence regarding depression symptoms related to endophenotypes, these findings still need to be interpreted with caution until directly replicated. Second, our data on the associations between genes, alcohol dependence, and depression were cross-sectional, thereby limiting internal validity. Third, due to the lack of measurement before the acute alcohol withdrawal, we could not rule out that *RETN* polymorphisms may have a more general role in moderating the relationship between alcohol dependence and depression. Moreover, data on body mass index (BMI) were lacking in this study to further explore the relationship between BMI and resistin gene polymorphisms, and whether BMI is correlated with depressive symptoms during alcohol withdrawal in alcohol-dependent adult men needs to be furtherly investigated. Finally, this study focused on male Chinese individuals and whether the results of this study are applicable to other groups still needs to be verified by future studies.

5 | CONCLUSION

In summary, the present study provides preliminary evidence for G×E interactions for depression symptoms, such that the *RETN* rs1477341 polymorphisms might correlate with susceptibility for depression symptoms of male alcohol-dependent adults during alcohol withdrawal. The findings support the hypothesis of the strong diathesis-stress model, in which the *A* alleles of *RETN* rs1477341 are a risk factor, regardless of environmental conditions (severity of alcohol dependence symptoms during withdrawal). These empirical findings indicate the potential contribution of *RETN* rs1477341 polymorphisms to the regulation of depression symptoms and might encourage more work at the molecular level on the role of the underlying mechanisms modulating depression. These findings promote the etiological understanding of depression, highlighting the complex effect of alcohol dependence and withdrawal on depression, and adding evidence supporting the relationship between Resistin gene and depression in male adults during acute alcohol withdrawal.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest (financial or otherwise) related to the data presented in this manuscript.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation. Requests to access these datasets should be directed to Fan Wang, fanwang@bjmu.edu.cn.

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APPENDIX A

TABLE A1 Interaction between RETN genotyping (rs1477341, rs3745368) and alcohol dependence on depression.

		Depression					
	Variables	**ΔR^2**	***B* (SE)**	***β***	***t***	***p***	**95% CI**
Step 1	Age	0.001	−0.001 (0.01)	−0.002	−0.04	0.97	−0.01, 0.01
	Educational years		0.001 (0.02)	0.01	0.21	0.83	−0.03, 0.04
Step 2	Alcohol dependence	0.06	0.24 (0.05)	0.24	4.88	<0.001***	0.14, 0.33
	rs1477341		0.01 (0.11)	0.01	0.11	0.91	−0.20, 0.22
	rs3745368		−0.06 (0.11)	−0.03	−0.58	0.56	−0.28, 0.15
Step 3	Alcohol dependence × rs1477341	<0.001	−0.04 (0.11)	−0.03	−0.37	0.71	−0.25, 0.17
	Alcohol dependence × rs3745368	0.001	−0.07 (0.11)	−0.06	−0.60	0.55	−0.28, 0.15

Note: Depression is measured by SDS, alcohol dependence is measured by MAST.

Abbreviations: CI, confidence interval; MAST, Michigan alcoholism screening test; SDS, self-rating depression scale; SE, standard error.

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.