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Clinical Indices of Familial Alcohol Use Disorder

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Abstract

Background—Alcohol use disorders (AUDs) are clinically heterogeneous and strongly influenced by familial/genetic factors. Can we identify specific clinical features of AUDs that index familial liability to illness?

Methods—In twins from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders meeting DSM-IV criteria for lifetime AUDs, we examined whether clinical features of AUDs, including individual DSM-IV criteria for alcohol dependence (AD) and alcohol abuse (AA), predicted risk for AUDs in cotwins and/or parents. Analyses of individual criterion were repeated controlling for the total number of endorsed criteria.

Results—Across these analyses, examining narrowly and broadly defined AUDs, risk of AUDs in relatives was more consistently predicted by abuse criteria than by dependence criteria, and by criteria reflecting negative psychosocial consequences rather than pharmacologic/biological criteria. Age at onset (AAO) poorly predicted risk in relatives. AUD associated legal problems, the one criterion slated for removal in DSM-5, was the most consistent single predictor of familial risk. Associations observed between individual criteria and risks of illness in relatives were generally stronger in monozygotic than dizygotic twin pairs, suggesting that these symptoms reflect a genetic risk for AUDs.

Conclusions—Individual DSM-IV criteria for AA and AD differ meaningfully in the degree to which they reflect the familial/genetic liability to AUDs. Contrary to expectation, the familial/genetic risk to AUDs was better reflected by symptoms of abuse and negative psychosocial consequences of AUD than by early AAO, or symptoms of tolerance and withdrawal.

Keywords

Alcohol Abuse; Alcohol Dependence; Twin Studies; Heritability; Symptoms

ALCOHOL USE DISORDER (AUD) is a clinically heterogeneous syndrome, as affected individuals vary widely in their age at onset (AAO), pattern of recurrence, and symptom profiles. While many studies document that the risk for AUD is strongly influenced by familial/genetic factors (e.g., Goodwin, 1981; Heath et al., 1997; Prescott and Kendler, 1999), these results reflect averages of a group of affected individuals. Individuals with AUD undoubtedly differ in the level of their underlying familial risk.

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In DSM-III (American Psychiatric Association, 1980), III-R (American Psychiatric Association, 1987), and IV (American Psychiatric Association, 1994), AUDs have consisted of 2 syndromes: alcohol abuse (AA) and alcohol dependence (AD). Their interrelationship has been controversial. The original conception was that abuse was a milder but largely independent syndrome that might evolve into dependence over time. Empirical results, however, have suggested that the symptoms of the 2 disorders are highly correlated and that the criteria for abuse are not at all “milder” than the dependence criteria (Saha et al., 2006).

A broad but significant question within the literature has been the degree to which an individual's familial vulnerability to AUDs can be meaningfully related to the clinical features of their AUD. This association has previously been investigated in studies that have compared the clinical features of familial and nonfamilial alcoholism (Alterman et al., 2002; Goodwin, 1984; Limosin et al., 2001; Penick et al., 1987). In this paper, we explore this question using a different approach. We begin by selecting individuals from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders (VATSPSUD) who meet lifetime criteria for AUD as assessed at personal interview. We then determine whether the clinical features of their AUDs as reported by these individuals (e.g., AAO, patterns of recurrence, treatment, and the presence or absence of individual AA and AD criteria) predict the risk of AUDs in their cotwin and in their parents.

The results of these analyses will have clinical, research, and nosological implications. For both clinical and research purposes, it would be useful to know, from the clinical features of their illness, which individuals with AUDs were likely to have a high versus low familial risk of illness. Nosologically, these analyses provide information about the validity of the individual diagnostic criteria. As the seminal article of Robins and Guze (1970), familial aggregation has been a key validator for psychiatric diagnoses. This approach would suggest that individual AUD criteria that index the familial risk for the disorder would be of particular diagnostic value.

MATERIALS AND METHODS

Participants in this study derived from 2 interrelated studies of Caucasian same-sex twin pairs who participated in VATSPSUD (Kendler and Prescott, 2006). All subjects were ascertained from the population-based Virginia Twin Registry formed from a systematic review of birth certificates in the Commonwealth of Virginia. Female–female (FF) twin pairs, born from 1934 to 1974, were eligible if both members responded to a mailed questionnaire in 1987 to 1988. Reports on symptoms of lifetime AD used in this report were collected at the fourth interview wave (FF4), conducted in 1995 to 1997. For this wave, we succeeded in interviewing 85% of eligible twins. Data on the male–male and male–female pairs (MMMF) came from a sample (birth years 1940 to 1974) initially ascertained directly from registry records containing all twin births. The first interview (MMMF1) was completed largely by phone in 1993 to 1996 and was followed by a second wave of interviews (MMMF2), conducted in 1994 to 1998, with a response rate of 83%. Data on symptoms of AD were used from the MMMF2 wave.

Zygosity was determined by discriminant function analyses using standard twin questions validated against DNA genotyping in 496 pairs (Kendler and Prescott, 1999). The mean (SD) age and years of education of the twins were 36.3 (8.2) and 14.3 (2.2) at the FF4 interview, and 37.0 (9.1) and 13.6 (2.6) at the MMMF2 interview.

The AUD section of our interview was adapted from the SCID (Spitzer et al., 1987) and modified to include expanded screening questions and DSM-IV criteria (American Psychiatric Association, 1994). In this version of the SCID, once a subject met screening

criteria for quantity of alcohol consumed or alcohol-related concerns or problems, all abuse and dependence criteria were systematically assessed with no skip-outs. Subjects, who did not make screening criteria because they were lifetime abstainers or light drinkers, were counted as unaffected in our analyses.

Lifetime AA and AD were diagnosed using DSM-IV criteria. AUD in the mother and father were diagnosed using the Family History Research Diagnostic Criteria (Endicott et al., 1975) from cotwin report. These criteria require the report of a sustained drinking problem and 1 or more of 6 criteria including legal, health, marital, social, and work problems associated with alcohol use, or treatment. They likely reflect a mixture of DSM-IV AA and AD, and so in this report, we refer to these family history diagnoses as AUDs.

We have previously seen in this sample that the presence of a disorder in an individual can alter the chances that person will report a family history of that same diagnosis in parents (Kendler et al., 1991). To avoid this kind of projection bias, we always examined the ability of symptoms of AUD in 1 twin to predict the history of AUDs in parents, as reported by the other twin of the pair.

We used in these analyses a total of 3,045 same and opposite sex twin pairs; 55.8% of the twins in these pairs were men and had a mean (SD) age at interview of 36.0 (8.8). In these pairs, 1,120 individual twins had a lifetime diagnosis of AD of whom 119 (10.6%) had a cotwin with AD. A total of 1,829 individuals from these pairs had a diagnosis of AA or AD of whom 425 (23.2%) had a cotwin with AA or AD. The risk for a family history diagnosis of AUDs in the parents of twins with AUDs (as reported by their cotwin) was 28.8% in fathers and 8.5% in mothers.

The human subject committees at Virginia Commonwealth University approved this project. Written informed consent was obtained prior to face-to-face interviews and verbal consent prior to phone interviews. Interviewers had a master's degree in a mental health-related field or a bachelor's degree in this area plus 2 years of clinical experience. At each wave, members of a twin pair were interviewed by different interviewers who were blind to clinical information about the cotwin.

Statistical Analyses

Our logistic regression analyses were run using PROC LOGISTIC in SAS (SAS Institute, 2007) where we predicted risk for AD in the cotwin and parents or a summary of genetic risk from cotwin and parents of "probands" twins with AD. Twin pairs that were concordant for a lifetime diagnosis of AD or AUD (which made up, respectively, 21.6 and 30.3% of all pairs) were double-counted in the appropriate analyses. We utilized a robust variance estimator to correct for the correlational structure of the data (Hindsberger and Bryld, 2003). In constructing a summary genetic risk, we calculated this as a within family prevalence of AUD weighting monozygotic (MZ) cotwins twice as much as dizygotic (DZ) cotwins who were weighted equally with mothers and fathers (because MZ twins share 100% of their genes identical by descent, while DZ twins and parent-offspring pairs share on average 50%).

We want to gain insight into the degree to which the observed association between clinical features of AUDs and risk for AUDs in relatives is a result of genetic versus familial-environmental factors. We are poorly powered to do formal interaction analyses. Therefore, we compared the observed significant associations run separately in MZ and DZ twin pairs. If we find that most or all of them have stronger effect sizes in the MZ pairs, we will interpret this as indicating that the clinical features are likely reflecting genetic risk to AUDs. If, by contrast, the observed associations are typically of similar magnitude in the 2

twin types, that would suggest that the clinical features are likely indexing familial-environmental risk to AUDs.

RESULTS

Prevalence of Individual Criteria in Subjects with Alcohol Dependence and Alcohol Dependence of Abuse

The endorsement frequency of individual DSM-IV criteria for AA and AD in the subjects meeting criteria for AD, and AA or AD are depicted in Table 1. In twins meeting criteria for AD, endorsement frequencies ranged from 16% (D7—use despite physical problems) to 93% (D3—loss of control). In twins that met criteria for AA or AD, endorsement frequencies were, as expected, moderately lower, ranging from 10% (D7—use despite physical problems) to 77% (D3—loss of control).

Alcohol Dependence

Table 2 depicts the results of our analyses selecting respondents who met DSM-IV criteria for AD ($n = 1,120$) and looking at what clinical features of AUDs predicted the risk for AD in cotwins. Using logistic regression analysis, we first predicted risk for AD in the cotwin, controlling for sex of the twin and cotwin, and zygosity. Taken one at a time, the risk for AD in the cotwin was positively predicted by the endorsement of all 4 of the abuse criteria, 2 dependence criteria (activities given up and use despite physical problems), the total number of endorsed criteria, a history of treatment for AD, and a long duration of the longest episode. The strongest predictors were 2 of the abuse criteria: hazardous use and legal problems.

We then repeated these analyses also controlling for the number of AA or AD criteria (except the one under examination) endorsed by the subject. Only the 2 abuse criteria (hazardous use and legal problems) remained significant predictors of risk of AD in the cotwin.

Alcohol Use Disorders

Table 3 depicts the results of our analyses selecting respondents who met DSM-IV criteria for AUDs (that is AA and/or AD) ($n = 1,829$) and looking at what clinical features of AUDs predicted the risk for AD in the cotwins and parents. Using our standard control variables, 3 of 4 abuse symptoms (failing obligations, hazardous use, and legal problems), 5 of 7 dependence criteria (tolerance, loss of control, time spent, activities given up, and use despite social problems), total number of endorsed criteria, and treatment history significantly predicted risk of AUDs in the cotwin. The strongest individual predictors were D6 (activities given up), A3 (legal problems), D5 (time spent), and A1 (failing obligations).

Repeating these analyses now controlling for the number of AA or AD criteria endorsed by the subject (except the one under examination), 3 criteria remained predictive. Two abuse criteria (failing obligations and hazardous use) predicted increased risk of AUDs in the cotwin, while 1 dependence criterion (withdrawal) surprisingly predicted a reduced risk for AUDs in the cotwin.

We then turned to examining which clinical features predicted AUDs in the parents of the twins with AUD. With our standard covariates, risk of AUDs in parents was significantly predicted by 2 of 4 abuse criteria (failing obligations and legal problems), 5 of 7 dependence criteria (withdrawal, loss of control, time spent, activities given up, and use despite physical problems), number of endorse criteria, treatment and a higher number of episodes. We then repeated these analyses with the additional control variable—the number of endorsed AA or

AD criteria (except the one under examination). Only 1 criterion remained a significant predictor: the abuse criterion of hazardous use.

Finally, we predicted risk for AUD in both the parents and cotwins. With our standard covariates, all the abuse and dependence criteria, the number of endorsed criteria, and treatment were significantly predictive. Repeating these analyses now controlling for the number of AA or AD criteria endorsed by the subject (except the one under examination), 3 criteria remained predictive. One abuse criterion (hazardous use) and 2 dependence criterion (activities given up and use despite physical problems) predicted increased risk of AUDs in the cotwin and parents.

Source of Familial Resemblance

To gain insight into the mechanism whereby these symptoms and clinical criteria predicted risk for AD or AUDs in the cotwin, we compared the magnitude of the observed association in MZ and DZ twin pairs in the 40 individually significant results from our standard regression analyses in cotwins presented in Tables 2 and 3. In 33 of these analyses, the association was stronger in MZ pairs, a result very unlikely to occur by chance ($p < 0.0001$).

DISCUSSION

The goal of these analyses was to clarify the degree to which individual clinical features of AUDs index the familial liability to illness. We operationalized this by examining the degree to which these clinical features in individuals with a diagnosis of AUDs predicted risk for AUDs in cotwins and parents. We performed these analyses twice: once in a narrowly defined group of affected twins who met lifetime criteria for AD, and second, in a broader group who met lifetime criteria for either AD or AA (whom we called AUD). In each group, we examined each criterion individually, both just with standard covariates (sex of twin, sex of cotwin, zygosity of twins), and then adding the number of other endorsed criteria. The latter analyses examined the specific predictive ability of the examined criterion controlling for overall clinical severity.

From this rather large number of results, 6 themes were noteworthy. First, one plausible a priori hypothesis—that criteria for AD would do a much better job than criteria for AA at reflecting familial risk to AUDs—was disproven. In nearly all the analyses, the reverse pattern was seen. Across our analyses, we had 8 individual findings where an endorsed criterion significantly increased risk for AD or AUD in relatives after including the number of other endorsed criteria as a covariate. Of these, 6 were with abuse criteria and only 2 with dependence criteria. Put another way, 3 of 4 abuse criteria versus 2 of 7 dependence criteria significantly predicted, in one or more analysis, an increased risk for AD or AUD in relatives after including the number of other endorsed criteria as a covariate.

Second, another somewhat related hypothesis was that the “pharmacological” criteria that assess tolerance and withdrawal, and that presumably best index the “biological processes” underlying alcohol addiction, would best index the familial vulnerability to AUDs. This was also disproven. The 2 criteria assessing tolerance and dependence (criteria D1 and D2) were among the most poorly performing criteria at predicting risk of AUDs in relatives.

Third, a number of prior studies indirectly suggest that early AAO should strongly index familial liability to AUDs (e.g., Babor et al., 1992; Hsu et al., 1990). In our analyses, AAO never predicted risk of AUDs in relatives. Fourth, across our multiple analyses, the criteria that predicted risk for AUDs controlling for overall severity (failing obligations, hazardous use, legal problems, activities given up, and use despite physical problems) tended to assess the negative psychosocial and medical sequelae of heavy alcohol use. While these symptoms

are often conceptualized as being more “down-stream” consequences of AUDs than “core” addiction symptoms, in our hands, they did a better job of indexing familial risk to AUDs.

Fifth, the current proposal from the DSM-5 Psychoactive Substance Use Disorder workgroup (<http://www.DSM5.org>) is to combine criteria for AA and AD together into a new Substance Use Disorder category. The proposal also calls for eliminating criterion A3 (legal problems associated with drug use) and add a criterion to assess craving. Our data are not supportive of this part of this proposal. Of all the abuse and dependence criteria across all of our analyses, criterion A3 is the most consistent predictor of risk for AUDs in relatives.

Sixth, our study was not designed (nor is it well powered) to determine whether individual AUD criteria are indexing familial risk as a result of genetic or shared environmental mechanisms. Nonetheless, we have some ability to address this question by comparing the degree to which these criteria predict risk more strongly in MZ versus DZ pairs. We found that in 33 of the 40 cases where significant results were found in our standard regression analyses, the association was stronger in the MZ pairs. This pattern of findings, very unlikely by chance alone, suggests that for most of our results, the clinical features of AUD that we are examining are indexing the genetic rather than the shared environmental risk to AUD. These results are consistent with the findings in this and other twin and adoption samples (Cloninger et al., 1981; Goodwin et al., 1974; Heath et al., 1997; Kendler et al., 1994, 1997; Prescott and Kendler, 1999; Sigvardsson et al., 1996) that resemblance for AUDs in twins, or between offspring and parents, is due largely to genetic factors.

How do our findings compare with the prior literature that has examined the clinical features of illness in individuals with AUD with a positive versus negative family history of alcoholism? In an early review, Goodwin (1984) emphasizes 2 main findings. Compared with nonfamilial alcoholism, familial alcoholism is associated with an early AAO and a severe course. In one of the most detailed such studies, Penick and colleagues compared 568 familial and nonfamilial alcoholics seen in a clinical setting on 17 “alcoholism symptoms.” They differed significantly on 7, with familial cases having higher rates of binges, black-outs, drinking arrests, loss of control, driving while intoxicated, loss of control, drinking at work, and drinking alcohol substitutes (Penick et al., 1987). In a much smaller study, Limosin and colleagues (2001) found the familial cases to have higher rates of interference with social activities and alcohol-related arrests. In the most comparable study we could find, Alterman and colleagues (2002) examined differences in rates of DSM-IV AA and AD criteria in 344 college-age men as a function of 3 levels of familial loading for alcoholism. They found significant associations between familial loading and criterion endorsement rates for 3 of 4 abuse criteria (all except hazardous use) and 5 of 7 dependence criteria (all except tolerance and withdrawal). With over 3,000 adult subjects from a representative epidemiological sample, our study was much larger than any prior investigation we could find, which attempted to associate family history for AUDs with individual symptoms or diagnostic criteria. Our results are inconsistent with some prior findings (e.g., on AAO). Interestingly, our results showing little association between symptoms of tolerance and withdrawal and familial risk for AUDs are congruent with the most comparable study (Alterman et al., 2002).

Prior gene finding efforts in AUDs by linkage, candidate gene association, or more recently genome-wide association have largely selected cases on the basis of DSM-IV criteria (e.g., Bierut et al., 2010; Edenberg et al., 2010; Prescott et al., 2006). Our results raise the question of whether those diagnostic criteria are optimal for selecting individuals with a high genetic liability to AUDs. Using analytic strategies such as the one pursued here, it might be

possible to arrive at a criteria set that would outperform standard approaches in selecting cases for molecular studies—that is those with particularly high genetic risk for AUDs.

Our findings do not fit closely into the large prior literature on typologies of AUDs (Babor, 1996; Morey and Blashfield, 1981) in part because of our sole focus on clinical features of AUDs as opposed to other features such as comorbidities or personality types. Our findings have some congruence with Cloninger's (1987) influential typology in which his type 2 AD (early onset and highly familial) was characterized by frequent arrests when drinking (indexed by criterion A3 that did predict risk in relatives) and infrequent loss of control (indexed by criterion D3 that was not predictive of risk for AUDs in relatives). Babor's type B AD was also characterized by high familial loading and early onset, and high levels of antisocial personality, which perhaps would be indexed by criterion A3 (Babor et al., 1992).

Limitations

These results should be interpreted in the context of 3 potentially significant methodological limitations. First, the sample is an epidemiological one. Therefore, the average severity of individuals making criteria for AUDs is likely to be considerably less than would be seen in clinically ascertained cohorts. Second, the symptoms are obtained retrospectively by semistructured interview. It is likely that the associations found in this report are attenuated by problems with reliability of recall. It is less likely that our results were created by recall bias because it is hard to imagine how certain symptoms of AUDs would be preferentially remembered only in subjects who had other individuals in their families with AUDs. Third, we did not examine many other features of subjects with AUDs that might predict risk of illness in their relatives such as comorbidities or prior personality. However, the focus of this manuscript was specifically on the limited number of features examined, especially DSM-IV criteria for AA and AD.

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Table 1

Prevalence of Individual DSM-IV Alcohol Dependence (AD) and Alcohol Abuse Criteria in Subjects with a Lifetime Diagnosis of AD and AD or Abuse

DSM-IV criteria	Prevalence in twins with AD		Prevalence in twins with AD or abuse	
	Count	Percent	Count	Percent
Abuse #1—Failing obligations	623	55.63	874	47.79
Abuse #2—Hazardous use	686	61.25	1068	58.39
Abuse #3—Legal problems	399	35.63	581	31.77
Abuse #4—Use despite social problems	730	65.18	1037	56.70
Dependence #1—Tolerance	882	78.75	1064	58.17
Dependence #2—Withdrawal	473	42.23	499	27.28
Dependence #3—Loss of control	1046	93.39	1409	77.04
Dependence #4—Trying to cut down	887	79.20	1068	58.39
Dependence #5—Time spent	882	78.75	1007	55.06
Dependence #6—Activities given up	377	33.66	392	21.43
Dependence #7—Use despite physical problems	179	15.98	188	10.28

Table 2

Prediction of Risk for Alcohol Dependence (AD) in the Cotwin from the Symptoms and Other Clinical Features of Alcohol Use Disorders in the Twin

Criteria in Twin	Odds ratio and 95% confidence intervals for prediction of AD in cotwin (<i>n</i> = 1,120)	
	Standard analyses	Including total criterion count ^a
Abuse #1—Failing obligations	1.31 [†] (1.01, 1.69)	0.98 (0.74, 1.30)
Abuse #2—Hazardous use	1.82 [#] (1.35, 2.45)	1.54 [‡] (1.12, 2.10)
Abuse #3—Legal problems	1.79 [#] (1.35, 2.37)	1.52 [‡] (1.13, 2.05)
Abuse #4—Use despite social problems	1.54 [‡] (1.16, 2.04)	1.20 (0.89, 1.62)
Dependence #1—Tolerance	1.07 (0.77, 1.47)	1.06 (0.76, 1.46)
Dependence #2—Withdrawal	1.16 (0.89, 1.52)	0.92 (0.68, 1.23)
Dependence #3—Loss of control	0.93 (0.55, 1.56)	0.90 (0.53, 1.53)
Dependence #4—Trying to cut down	1.09 (0.79, 1.52)	1.06 (0.76, 1.48)
Dependence #5—Time spent	1.29 (0.93, 1.78)	1.13 (0.81, 1.57)
Dependence #6—Activities given up	1.55 [‡] (1.18, 2.03)	1.24 (0.93, 1.65)
Dependence #7—Use despite physical problems	1.76 [*] (1.26, 2.46)	1.42 (1.00, 2.01)
Number of alcohol abuse (AA) or AD criteria	1.17 [#] (1.10, 1.25)	
Treatment	1.39 [†] (1.04, 1.86)	
Number of episodes	0.99 (0.96, 1.02)	
Age at onset (symptoms)	0.98 (0.95, 1.00)	
Longest duration (years)	1.00 (1.00, 1.01)	

Control variables: sex of twin, sex of cotwin, zygosity of twins.

^a Additional control variable: number of endorsed AA or AD criteria (excluding prediction variable). Significance:

[†] *p* 0.05,

[‡] *p* 0.01,

^{*} *p* 0.001,

[#] *p* 0.0001.

Table 3

Prediction of Risk for Alcohol Use Disorders (Abuse and/or Dependence) in the Cotwin and Parents from the Symptoms and Other Clinical Features of Alcohol Use Disorders in the Twin

Criteria in twin	Odds ratio and 95%confidence intervals for prediction of alcohol abuse (AA) or dependence in cotwin (n = 1,829)		Odds ratio and 95%confidence intervals for prediction of alcohol dependence (AD) in parent (n = 1,706)		Odds ratio and 95%confidence intervals for prediction of AD in cotwin or parent (n = 1,804)	
	Standard analyses	Including total criterion count ^a	Standard analyses	Including total criterion count ^a	Standard analyses	Including total criterion count ^a
Abuse #1—Failing obligations	1.51 [#] (1.24, 1.84)	1.28 [†] (1.04, 1.58)	1.27 [†] (1.03, 1.56)	1.09 (0.88, 1.37)	1.37 [*] (1.15, 1.64)	1.07 (0.88, 1.29)
Abuse #2—Hazardous use	1.34 [†] (1.09, 1.65)	1.21 (0.98, 1.50)	1.15 (0.92, 1.44)	1.05 (0.84, 1.31)	1.28 [†] (1.06, 1.54)	1.12 (0.93, 1.35)
Abuse #3—Legal problems	1.67 [#] (1.34, 2.08)	1.50 [*] (1.19, 1.88)	1.55 [*] (1.23, 1.95)	1.42 [†] (1.12, 1.80)	1.78 [#] (1.47, 2.16)	1.55 [#] (1.28, 1.88)
Abuse #4—Use despite social problems	1.20 (0.99, 1.47)	0.98 (0.79, 1.21)	1.14 (0.93, 1.41)	0.96 (0.77, 1.20)	1.44 [#] (1.20, 1.73)	1.14 (0.94, 1.38)
Dependence #1—Tolerance	1.31 [†] (1.07, 1.60)	1.01 (0.82, 1.26)	1.08 (0.87, 1.33)	0.91 (0.73, 1.13)	1.29 [†] (1.06, 1.56)	1.02 (0.84, 1.24)
Dependence #2—Withdrawal	1.23 (0.98, 1.54)	0.74 [†] (0.57, 0.95)	1.28 [†] (1.01, 1.62)	1.00 (0.76, 1.31)	1.41 [*] (1.15, 1.74)	0.94 (0.75, 1.19)
Dependence #3—Loss of control	1.28 [†] (1.01, 1.62)	0.92 (0.71, 1.18)	1.49 [†] (1.15, 1.93)	1.28 (0.98, 1.68)	1.55 [*] (1.23, 1.95)	1.20 (0.95, 1.52)
Dependence #4—Trying to cut down	1.15 (0.94, 1.41)	0.85 (0.69, 1.06)	1.16 (0.94, 1.44)	0.99 (0.79, 1.24)	1.37 [†] (1.13, 1.65)	1.08 (0.89, 1.32)
Dependence #5—Time spent	1.59 [#] (1.30, 1.94)	1.14 (0.91, 1.43)	1.42 [†] (1.14, 1.76)	1.20 (0.94, 1.53)	1.55 [#] (1.28, 1.88)	1.15 (0.94, 1.42)
Dependence #6—Activities given up	1.77 [#] (1.39, 2.25)	1.17 (0.89, 1.53)	1.57 [*] (1.23, 2.00)	1.29 (0.97, 1.71)	1.90 [#] (1.53, 2.35)	1.35 [†] (1.07, 1.72)
Dependence #7—Use despite physical problems	1.38 [†] (1.00, 1.90)	0.85 (0.61, 1.19)	1.48 [†] (1.08, 2.04)	1.16 (0.82, 1.63)	2.03 [#] (1.54, 2.67)	1.41 [†] (1.06, 1.89)
Number of AA or AD symptoms	1.13 [#] (1.08, 1.18)		1.10 [#] (1.05, 1.15)		1.16 [#] (1.12, 1.20)	
Treatment	1.50 [†] (1.18, 1.91)		1.80 [#] (1.40, 2.31)		1.75 [#] (1.41, 2.16)	
Number of episodes	0.98 (0.95, 1.01)		1.04 (1.00, 1.09)		1.01 (0.98, 1.03)	
Age at onset (symptoms)	0.99 (0.97, 1.01)		1.01 (0.99, 1.03)		1.00 (0.99, 1.02)	
Longest duration (years)	1.00 (1.00, 1.00)		1.00 (1.00, 1.01)		1.00 (1.00, 1.00)	

Control variables: sex of twin, sex of cotwin, zygosity of twins.

^a Additional control variable: number of endorsed AA or AD criteria (excluding prediction variable). Significance:

[†] *p* 0.05,

[‡] *p* 0.01,

^{*} *p* 0.001,

[#] *p* 0.0001.