

Tests of Causal Links Between Alcohol Abuse or Dependence and Major Depression

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Context: There has been a great deal of research on the comorbidity between alcohol abuse or dependence (AAD) and major depression (MD). However, it is unclear whether AAD increases the risk of MD or vice versa.

Objective: To examine the associations between AAD and MD using fixed-effects modeling to control for confounding and using structural equation models to ascertain the direction of causality.

Design: Data were gathered during the course of the Christchurch Health and Development Study, a 25-year longitudinal study of a birth cohort of children from New Zealand (635 boys, 630 girls).

Setting: General community sample.

Participants: The analysis was based on a sample of 1055 participants with available data on AAD and MD at ages 17 to 18, 20 to 21, and 24 to 25 years.

Main Outcome Measures: Symptom criteria for AAD and MD from the DSM-IV at ages 17 to 18, 20 to

21, and 24 to 25 years as well as measures of life stress, cannabis use, other illicit drug use, affiliation with deviant peers, unemployment, partner substance use, and partner criminality at ages 17 to 18, 20 to 21, and 24 to 25 years.

Results: There were significant ($P < .001$) pooled associations between AAD and MD. Controlling for confounding factors using conditional fixed-effects models and time-dynamic covariate factors reduced the magnitude of these associations, but they remained statistically significant. Structural equation modeling suggested that the best-fitting causal model was one in which AAD led to increased risk of MD.

Conclusions: The findings suggest that the associations between AAD and MD were best explained by a causal model in which problems with alcohol led to increased risk of MD as opposed to a self-medication model in which MD led to increased risk of AAD.

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IN RECENT DECADES, A LARGE NUMBER of studies have examined the comorbidity of a range of mental disorders.¹⁻³ One comorbidity that has been examined in detail is the association between alcohol abuse or dependence (AAD) and major depression (MD).⁴⁻⁶ A number of epidemiological studies have shown that AAD is frequently comorbid with MD.⁷⁻¹⁷

The apparent comorbidity between AAD and MD may be explained in at least 2 ways. First, it could be argued that both AAD and MD are caused by common underlying genetic and environmental factors. Indeed, a number of studies have found evidence of shared genetic and environmental influences in the comorbidity of AAD and MD.¹⁸⁻²³ However, some studies have also found evidence for residual associations between AAD and MD after controlling for shared genetic and en-

vironmental influences,¹⁸⁻²¹ suggesting that there may be an association between these disorders that cannot be accounted for by common confounding factors.

Second, it could be argued that AAD and MD are related in a causal manner such that either MD increases the risk of AAD or AAD increases the risk of MD. Indeed, studies have claimed that AAD may arise as a result of self-medication of depressive symptoms.^{13,19,24} Other studies, however, have suggested that AAD increases the risk of MD.^{14,25,26}

CONTROLLING RESIDUAL CONFOUNDING WITH THE FIXED-EFFECTS REGRESSION MODEL

Although it is often believed that epidemiological research can only control for the effects of observed confounders, this

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is not strictly correct and there are a number of analytical approaches that permit the control of nonobserved confounders in nonexperimental research. The best known of these is the so-called discordant twin design in which monozygotic twins who are discordant for some exposure variable (eg, AAD) are compared on an outcome measure (eg, MD). Because the twin pairs share both common genes and common environment, this comparison controls for these factors.²²

The principles underlying the discordant twin design can also be applied to longitudinal data on singletons via the fixed-effects regression model. Subject to the availability of longitudinal data, it proves possible to estimate the associations between a time-varying exposure variable (such as AAD) and a time-varying outcome measure (such as MD) net of any nonobserved fixed factors that are associated with the outcome and that may be correlated with the exposure variable. In effect, this model makes it possible to eliminate one major source of confounding from fixed factors. However, the model does not address the issue of confounders that may vary over time; to control for such confounding, the fixed-effects model needs to be augmented by observed time-dynamic confounding factors.

ASCERTAINING CAUSAL DIRECTION USING STRUCTURAL EQUATION MODELING

Establishing that AAD and MD are related even following control for confounding is an important step in ascertaining a causal relationship between AAD and MD. However, such analysis does not resolve the issue of the direction of causality: even with well-collected longitudinal data, establishing which factor is antecedent and which factor is consequent proves difficult.²⁷ Furthermore, there is a possibility that AAD and MD are reciprocally related to each other by a feedback loop in which AAD increases risk of MD while at the same time the onset of MD leads to an increased consumption of alcohol.²⁴ Structural equation models provide one means to address this issue by devising statistical models that permit reciprocal relationships between AAD and MD and using these models to provide a guide to likely patterns of causation.

In this article, we address these issues using data gathered over the course of a longitudinal study in which measures of MD and AAD were obtained at regular intervals. In the first stage of the analyses, fixed-effects regression modeling was used to control the associations between AAD and MD for common confounding factors, including non-observed common genes and environment. In the second stage, methods of structural equation modeling were used to explore the direction of causality.

METHODS

PARTICIPANTS

The data were gathered during the course of the Christchurch Health and Development Study. In this study, a birth cohort of 1265 children (635 boys, 630 girls) born in the Christchurch, New Zealand, urban region in mid-1977 was studied at birth, age 4

months, and age 1 year, annually to age 16 years, and again at ages 18, 21, and 25 years.^{28,29} All study information was collected on the basis of signed consent from study participants.

AAD AND MD AT AGES 17 TO 18, 20 TO 21, AND 24 TO 25 YEARS

At ages 18, 21, and 25 years, study participants were interviewed on a structured mental health interview designed to assess aspects of mental health and psychosocial adjustment. In these assessments, components of the Composite International Diagnostic Interview³⁰ were used to assess DSM-IV symptom criteria for a range of disorders including AAD and MD using the full range of questions pertaining to AAD and MD. Participants who met criteria for AAD and/or MD during the year prior to assessment (at ages 17-18, 20-21, and 24-25 years) were classified as having had AAD and/or MD during that period. In addition, for the purposes of structural equation modeling, participants were classified on 3-level ordinal scale measures reflecting the severity of MD or AAD symptoms in each interval. For MD, 0 indicated that the participant had no depressive symptoms; 1, the participant had depressive symptoms but did not meet criteria for MD; and 2, the participant met criteria for MD. For AAD, 0 indicated that the participant had no alcohol-related problems; 1, the participant reported symptoms of AAD but did not meet criteria for alcohol dependence; and 2, the participant met criteria for alcohol dependence.

TIME-DYNAMIC COVARIATE FACTORS

The following time-dynamic covariate factors were chosen from the database of the study on the basis of their associations with either AAD or MD in preliminary analyses and of previous research examining AAD and MD among the present cohort.^{31,32} These covariate factors included the following, and each were assessed during the periods when the participants were aged 17 to 18, 20 to 21, and 24 to 25 years.

Stressful life events were assessed by responses to items from the Feeling Bad Scale³³ and custom-written survey items to provide an index of the number of stressful life events during each year. Cannabis use was assessed at each year by questioning the frequency with which participants had used cannabis during each year since the previous assessment. Other illicit drug use was assessed at each year by questioning whether the participants had used illicit drugs other than cannabis during each year since the previous assessment. Affiliation with deviant peers was assessed via questions pertaining to friends' use of alcohol, tobacco, or other illicit drugs, involvement in criminal activity, problems with aggressive behavior, or being in trouble with the law in the year prior to each assessment. Unemployment was assessed by asking participants about their experience of unemployment in each year and was classified into 4 levels reflecting the duration of unemployment in the year. Partner substance use and criminal offending were assessed on the basis of participant reports of the extent to which their partner (1) used tobacco, alcohol, or illicit drugs or had problems resulting from alcohol or illicit drugs and (2) engaged in criminal offending, had problems with aggressive behavior, or was in trouble with the law.

STATISTICAL ANALYSIS

Associations Between AAD and MD

In the first stage of the analysis, the association between AAD and MD in each year was assessed using a logistic regression model in which the risk of MD was modeled as a logit function of AAD. In each case, the significance of the association

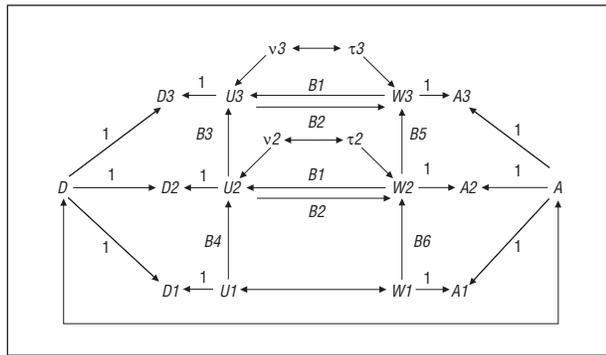


Figure. Autoregressive model of major depression and alcohol abuse or dependence symptoms incorporating fixed-effects and reciprocal paths between time-dynamic components of major depression and alcohol abuse or dependence symptoms. Dt indicates major depression symptoms at time t ; D , fixed-effects component of Dt ; U_t , time-dynamic component of Dt ; v_t , disturbance term for U_t ; A_t , alcohol abuse or dependence symptoms at time t ; A , fixed-effects component of A_t ; W_t , time-dynamic component of A_t ; and τ_t , disturbance term for W_t . Time t is shown as 1, 2, or 3, where $t=1$ for ages 17 to 18 years, $t=2$ for ages 20 to 21 years, and $t=3$ for ages 24 to 25 years.

was assessed using the Wald χ^2 statistic for the effect of AAD from the fitted model. In addition, the pooled association between AAD and MD was estimated via generalized estimating equation methods^{34,35} to fit a population-averaged regression model in which the risk of MD at each of the 3 periods was modeled as a logit function of AAD during each period. This model was of the following form: $\text{logit}(Y_{it}) = B_0 + B_1 X_{it}$, where $\text{logit}(Y_{it})$ was the log odds of MD reported by the i th subject in a given interval t , and X_{it} represented AAD during the interval t . In this model, observations from the same individual over time were permitted to be correlated with an unstructured correlation matrix. In addition, the associations were modeled using MD as the exposure variable and AAD as the outcome variable. All of the models were fitted using Stata version 8.0 statistical software (Stata Corp, College Station, Texas).

From the fitted models, estimates of the odds ratios (ORs) and 95% confidence intervals (CIs) of MD for AAD were calculated relative to those individuals who did not report AAD. In addition, the model in the earlier equation was both stratified by sex and expanded to incorporate sex \times AAD interactions in order to test for sex differences in the association between AAD and MD.^{22,24,36}

Fixed-Effects Model for Covariate Adjustment

To adjust the associations between AAD and MD for unobserved fixed and observed time-dynamic confounding factors, a conditional fixed-effects logistic regression model was fitted to the joint data over the 3 measurement periods. This model was of the following form: $\text{logit}(Y_{it}) = \alpha_i + B_1 X_{it} + \sum B_k Z_{ikt}$. In this model, the α_i values are individual specific terms assumed to reflect the effects of all fixed sources of variation in the outcome Y_{it} , and the Z_{ikt} values are the set of observed time-dynamic covariates. The fixed-effects α_i values are assumed to be constant over time and to be correlated with other predictors in the model. The major advantage of the fixed-effects model is that it can adjust for all sources of fixed covariate effects, including nonobserved fixed confounders.³⁷ In addition to this model, the fixed-effects models were also fitted using MD as the exposure variable and AAD as the outcome variable.

Structural Equation Modeling

To explore issues of causal direction, a series of structural equation models was fitted to the categorical measures of MD and

AAD symptoms observed for the 3 intervals from ages 17 to 18, 20 to 21, and 24 to 25 years. These models incorporated both fixed effects influencing the measures of MD and AAD over time and the potential to examine both unidirectional and reciprocal effects between MD and AAD within time intervals.

The **Figure** depicts a model with reciprocal causal effects between MD and AAD. This model assumed the following: (1) the observed symptom measures of MD (denoted Dt , with $t=1, 2, 3$) at ages 17 to 18 years ($t=1$), 20 to 21 years ($t=2$), and 24 to 25 years ($t=3$) were influenced by fixed sources of variation (D) that were constant over time and by time-dynamic sources of variation (U_t); (2) the observed symptom measures of AAD (denoted A_t , with $t=1, 2, 3$) were also influenced by fixed sources of variation (A) that were constant over time and time-dynamic sources of variation (W_t); (3) the fixed factors D and A were permitted to be correlated; (4) the time-dynamic components of depressive symptoms (U_t) and AAD symptoms (W_t) were linked by autoregressive processes in which past MD symptoms predicted future MD symptoms and in which past AAD symptoms predicted future AAD symptoms, respectively; (5) the time-dynamic components of MD and AAD symptoms were reciprocally related at $t=2$ or 3 so that current U_t influenced current W_t and vice versa, with these reciprocal effects assumed to be constant over time; and (6) the time-dynamic components U_1 and W_1 were assumed to be correlated rather than reciprocally related in order to assist with model identifiability.

In this model, the fixed effects (D, A) are latent variables that summarize the net effect of all nonobserved fixed factors that exert a constant effect on the measures of MD and AAD, respectively, over time. These factors include all childhood, family, and personal characteristics that have a fixed effect on outcomes over time; thus, they may include both genetic and environmental influences. The time-dynamic components of the model (U_t, W_t) represent the effect of all other sources of variance in MD and AAD, respectively, that are not solely due to fixed factors. The equations defining this model were as follows. For the model equations: $Dt = D + U_t$ ($t=1, 2, 3$); $A_t = A + W_t$ ($t=1, 2, 3$); $U_3 = B1W_3 + B3U_2 + v_3$; $W_3 = B2U_3 + B5W_2 + \tau_3$; $U_2 = B1W_2 + B4U_1 + v_2$; and $W_2 = B2U_2 + B6W_1 + \tau_2$. For the model assumptions: $\text{cov}(D, U_t) = \text{cov}(D, W_t) = \text{cov}(A, U_t) = \text{cov}(A, W_t) = 0$ ($t=1, 2, 3$); $\text{cov}(D, v_t) = \text{cov}(D, \tau_t) = \text{cov}(A, v_t) = \text{cov}(A, \tau_t) = 0$ ($t=2, 3$); $\text{cov}(v_t, \tau_s) = \text{cov}(v_t, v_s) = \text{cov}(\tau_t, \tau_s) = 0$ for $t \neq s$ ($t, s=2, 3$); $\text{cov}(D_t, v_s) = \text{cov}(D_t, \tau_s) = \text{cov}(A_t, v_s) = \text{cov}(A_t, \tau_s) = 0$ for $t < s$; and $\text{cov}(U_t, v_s) = \text{cov}(U_t, \tau_s) = \text{cov}(W_t, v_s) = \text{cov}(W_t, \tau_s) = 0$ for $t < s$. In these equations, the terms v_t and τ_t ($t=2, 3$) represent disturbance terms reflecting unexplained sources of variation in the time-dynamic components of MD symptoms (U_t) and AAD symptoms (W_t), respectively. The coefficients $B1$ and $B2$ represent the reciprocal effects of AAD on MD symptoms and vice versa, respectively, within each period. The coefficients $B3$ and $B4$ represent the across-time stabilities in the time-dynamic components of MD symptoms, and the coefficients $B5$ and $B6$ represent the across-time stabilities in the time-dynamic components of AAD symptoms.

The reciprocal cause model depicted in the **Figure** was fitted to the observed measures of MD and AAD symptoms at ages 17 to 18, 20 to 21, and 24 to 25 years. The fit of this model was then compared with the fit of 2 other models that assumed unidirectional causal effects between MD and AAD symptoms. These models were as follows: (1) a model that assumed a unidirectional effect from AAD to MD symptoms (ie, $B1 \neq 0$; $B2 = 0$), and (2) a model that assumed a unidirectional effect from MD symptoms to AAD symptoms (ie, $B1 = 0$; $B2 \neq 0$).

The models were fitted using the techniques described by Muthén³⁸ for ordered categorical data assuming an underlying multivariate normal distribution of the MD and AAD symptom report data with Mplus software³⁹ and the method of weighted least squares. Model goodness of fit was assessed on the basis of a num-

ber of indices, including the model χ^2 goodness-of-fit statistic, the root mean squared error of approximation (values of the root mean squared error of approximation < 0.05 are assumed to be indicative of a well-fitting model), and the Comparative Fit Index (this index varies between 0 and 1, with values close to 1 indicating a well-fitting model).⁴⁰

SAMPLE SIZE AND SAMPLE BIAS

The present analyses are based on the sample of 1055 participants for whom data on AAD and MD were available on at least 1 occasion from ages 18, 21, and 25 years. However, because not all of the participants were assessed at all of the ages, the observed sample numbers varied between age 18 years ($n = 1025$), age 21 years ($n = 1011$), and age 25 years ($n = 1003$). These samples represented between 79.3% and 81.0% of the initial cohort of 1265 participants.

To adjust for possible sample selection bias resulting from sample attrition, a 2-stage process was used. In the first instance, a sample selection model was constructed by using data gathered at birth to predict inclusion in the analysis sample. This showed that there were statistically significant ($P < .05$) tendencies for the obtained sample to underrepresent children from more socially disadvantaged backgrounds (low parental education, low socioeconomic status, single-parent family). On the basis of the fitted selection models, the sample was then poststratified into a series of groups and the probability of study participation was estimated for each group.

For the logistic regression models, the data were then re-analyzed with the observations for each individual weighted by the inverse of the probability of study participation and using standard error estimates that were robust to the weighting procedures used. For the structural equation models, analyses were conducted that both assumed missing observations within the analysis sample were missing at random and weighted the observed data by the inverse of the probability of study participation. The analyses were conducted using weighted least squares procedures that were robust to the data weighting and missing data assumptions.³⁹ In all cases, the analyses produced conclusions essentially identical to the findings reported here, suggesting that the effects of missing data and selection bias on the results were likely to be minimal.

RESULTS

RATES OF AAD AND MD AT AGES 17 TO 25 YEARS

At ages 17 to 18 years, 19.4% of the sample met criteria for AAD (5.7% for alcohol dependence, 13.7% for alcohol abuse) and 18.2% met criteria for MD. At ages 20 to 21 years, 22.4% met criteria for AAD (5.9% for alcohol dependence, 16.5% for alcohol abuse) and 18.2% met criteria for MD. Also, at ages 24 to 25 years, 13.6% met criteria for AAD (5.5% for alcohol dependence, 8.1% for alcohol abuse) and 13.8% met criteria for MD.

ASSOCIATIONS BETWEEN AAD AND MD AT AGES 17 TO 25 YEARS

Table 1 shows the ORs and 95% CIs for the associations between AAD and MD at ages 17 to 18, 20 to 21, and 24 to 25 years. In addition, Table 1 shows the population-averaged OR for the association between AAD and MD pooled over the 3 observation periods (see “Methods”).

Table 1. Odds Ratios and 95% Confidence Intervals for the Associations Between Alcohol Abuse or Dependence and Major Depression at Ages 17 to 18, 20 to 21, and 24 to 25 Years

Age, y	OR for MD (95% CI)	Wald χ^2 P Value
17-18	2.15 (1.50-3.08)	<.001
20-21	1.87 (1.31-2.66)	<.001
24-25	1.99 (1.26-3.12)	.003
Population-averaged	1.90 (1.53-2.37)	<.001

Abbreviations: CI, confidence interval; MD, major depression; OR, odds ratio.

At all ages there were clear and statistically significant trends ($P < .01$) for AAD to be associated with increased risk of MD. The population-averaged model suggested that individuals who fulfilled the criteria for AAD were 1.90 times (95% CI, 1.53-2.37) more likely to also fulfill the criteria for MD. In addition, pooled models in which AAD was regressed on MD produced comparable results (OR=1.93; 95% CI, 1.55-2.41).

Stratification of the models by sex and tests of sex \times exposure interaction using the full sample for both sets of models revealed no evidence of sex effects in the association between AAD and MD.

ADJUSTMENT FOR COVARIATE FACTORS

The associations between AAD and MD were adjusted for nonobserved genetic and environmental factors using fixed-effects regression methods. Fixed-effects models were fitted to the data for AAD and MD at ages 17 to 18, 20 to 21, and 24 to 25 years and extended to include a series of observed time-dynamic covariate factors measured during the period between ages 17 and 25 years (see “Methods”). Adjustment for fixed and time-dynamic covariate factors reduced the magnitude of the pooled association between AAD and MD (OR=1.66; 95% CI, 1.08-2.55; $P = .02$), but the association remained statistically significant. In addition, fixed-effects models with time-dynamic covariate factors in which AAD was regressed on MD produced comparable results (OR=1.59; 95% CI, 1.03-2.46; $P = .02$).

RESULTS FROM STRUCTURAL EQUATION MODELS

The findings are consistent with the view that AAD and MD may be linked by a cause and effect model. However, the analysis does not establish that this association is one in which increasing frequency of AAD symptoms leads to increased frequency of MD symptoms or vice versa. To address this issue, a series of structural equation models was fitted to the data to test alternative assumptions about the direction of association between AAD and MD (see “Methods”). Specifically, 3 models were fitted: (1) model 1, a model assuming a reciprocal association between MD and AAD within time; (2) model 2, a model assuming a unidirectional causal effect from AAD to MD; and (3) model 3, a model assuming a unidirectional effect from MD to AAD.

Table 2. Summary of Fitted Model Coefficients for the Causal Associations Between Major Depression and Alcohol Abuse or Dependence Symptoms and Model Goodness-of-Fit Indices

Model	Model Parameter		Goodness-of-Fit Indices				
	B (SE)	P Value	χ^2	df	P Value	RMSEA	CFI
Model 1, reciprocal effects			6.17	5	.29	.015	.997
Effect of AAD on MD (<i>B1</i>)	.292 (.098)	.003					
Effect of MD on AAD (<i>B2</i>)	-.092 (.081)	.26					
Model 2: unidirectional			7.35	6	.29	.015	.997
Effect of AAD on MD (<i>B1</i>)	.210 (.057)	<.001					
Model 3: unidirectional			16.99	6	.01	.042	.976
Effect of MD on AAD (<i>B2</i>)	.128 (.054)	.02					

Abbreviations: AAD, alcohol abuse or dependence; CFI, Comparative Fit Index; MD, major depression; RMSEA, root mean squared error of approximation.

tional causal effect from MD to AAD. In fitting these models, the correlations shown in the Figure between the disturbance terms νt and τt were fixed to 0 as preliminary analyses showed that these coefficients were nonsignificant for all of the models and at all of the times.

Table 2 shows estimates of the effects of AAD and MD on each other and associated goodness-of-fit statistics from the 3 models. The analyses suggested the following conclusions. First, models 1 and 2 were well fitting and led to the same general conclusion: AAD was significantly related to MD ($P = .003$) but MD was not significantly related to AAD ($P = .26$). The difference in χ^2 statistics for the 2 models was not statistically significant ($\Delta\chi^2 = 1.18$; $P = .28$), suggesting that the path from MD to AAD could be constrained to 0 without affecting model fit. Consistent with these results, model 3 was significantly less well fitting than models 1 and 2. In particular, the change in model χ^2 from models 1 to 3 was highly significant ($\Delta\chi^2 = 10.82$; $P = .001$), suggesting that the pathway from AAD to MD could not be constrained to 0 without affecting model fit.

As noted in "Methods," these estimates were obtained from a weighted least squares analysis fitted to an estimated matrix of polychoric correlations derived using ordered categorical measures of AAD and MD symptoms. To examine the sensitivity of the results to model estimation methods, a series of alternative models was fitted to the data. These included models using continuous count measures of *DSM-IV* symptom criteria for AAD or MD in each year, models based on *DSM-IV* diagnoses rather than ordered symptom categories, and models that excluded alcohol abuse criteria from the measures of alcohol problems and used only alcohol dependence symptoms. All of the models produced results consistent with the conclusions drawn as discussed earlier.

COMMENT

In this analysis, we have used data gathered over the course of a longitudinal study to examine the comorbidities of MD and AAD. The analysis used advanced statistical modeling methods to control for nonobserved sources of confounding and to explore causal pathways. The analysis led to the following conclusions.

First, in confirmation of previous research,⁷⁻¹⁷ there was evidence of significant comorbidity between AAD and

MD (pooled OR = 1.90; 95% CI, 1.53-2.37). Second, adjustment for nonobserved fixed sources of confounding and observed time-dynamic covariate factors showed that the association between MD and AAD could not be explained by these sources of confounding (adjusted OR = 1.66; 95% CI, 1.08-2.55). In addition, further analyses in which AAD was regressed on MD produced similar estimates. These findings are consistent with previous research using twin and other research designs that have concluded that the comorbidity between AAD and MD cannot be explained by common sources of confounding, including common genes and common environment.^{13,14,18-21,24-26} These findings are also consistent with the view that there likely is a direct cause and effect association between AAD and MD.

To explore possible pathways between AAD and MD, methods of structural equation modeling were used to fit a reciprocal causation model. This analysis suggested that the best-fitting model was one in which there was a unidirectional association from AAD to MD but no reverse effect from MD to AAD. Collectively this evidence is consistent with the conclusion that there is a cause and effect relationship between AAD and MD in which AAD leads to MD.^{14,25,26} The underlying mechanisms that give rise to such an association are unclear; however, it has been proposed that this link may arise from genetic processes in which the use of alcohol acts to trigger genetic markers that increase the risk of MD.^{41,42} In addition, further research suggests that alcohol's depressant characteristics may lead to periods of depressed affect among those with AAD.⁹

It should also be noted that the findings of this study are not in agreement with findings in a number of studies that have suggested a causal pathway from MD to AAD.^{13,19,24} There are several reasons why the findings may differ from those of other studies. First, other studies have used retrospective recall,^{13,17,19} whereas our study was prospective in nature. Second, at least 1 study modeled the first episode of MD and AAD,¹⁹ another study modeled the associations between MD and AAD at a single point in time,¹³ and our study modeled all of the instances of each disorder in 3 periods. Finally, a further study found evidence for a causal link from MD to AAD for female participants but not for male participants.²⁴

The findings of our study are also not in agreement with a recent US general population study by Grant et al,¹⁷ which

failed to find association between MD at wave 1 and AAD at wave 2 (approximately 3 years later) or between AAD at wave 1 and MD at wave 2. Again, however, methodological differences between that study and ours may account for the discrepant findings. For example, in the study by Grant and colleagues, wave 1 data were obtained via retrospective recall, wave 2 incidence data were limited to new-onset cases of AAD and MD, and the study controlled for observed confounding factors.

Our study did not find evidence for sex effects in the association between AAD and MD, again in disagreement with several other studies.^{22,24,36} The reasons for the difference in findings is unclear, but it could be argued that differences in social contexts or the age of participants may account for the fact that our study found no evidence to suggest sex differences in the association between AAD and MD.

It should also be noted that because the rates of alcohol abuse were higher than those for alcohol dependence, it could be argued that the causal links between AAD and MD may be largely due to symptoms of alcohol abuse. This in turn implies that the causal links between AAD and MD may be due to stressful life circumstances arising from the problematic use of alcohol, including problems with family and friends, financial issues, or legal issues. However, further research is required to elucidate the nature of the possible links between alcohol abuse and MD.

It is important to recognize that the conclusions drawn in this analysis rely on some underlying assumptions that are necessary to identify the models we have presented. The most pervasive of these assumptions is that the pattern of comorbidity being studied is represented by a stable causal process that was operative throughout the course of this study. This is clearly a strong assumption, but it is essential for both the fixed-effects and reciprocal-causes models. Additional research may be required to examine whether the assumptions regarding the stability of patterns of comorbidity between AAD and MD are correct. Furthermore, it is likely that the causal models we have used to represent these data are only approximations to a more complex set of conditions. For these reasons, our findings should be viewed as suggestive rather than definitive. Finally, it should also be noted that this study measured depressive episodes and was thus unable to examine the extent to which links between AAD and MD may have been influenced by bipolar disorder.⁴³

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