

Common Genetic Risk Factors for Conduct Disorder and Alcohol Dependence

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The association between retrospectively reported childhood conduct disorder (CD) and a history of alcohol dependence (AD) was examined in a sample of 2,682 male, female, and unlike-sex adult twin pairs. There was a strong association between CD and AD in both men (tetrachoric $r = .34$, odds ratio = 2.8) and women (tetrachoric $r = .53$, odds ratio = 9.9). Genetic factors accounted for most of the association between CD and AD liability in men and women, with the remainder of the association being due to nonshared individual-specific environmental factors. Genetic influences common to CD and AD accounted for 17% and 35% of the genetic variation in AD liability in men and women, respectively, and accounted for 11% and 23% of the total variation in AD liability in men and women, respectively. The results suggest that there are common genetic risk factors for CD and AD or that CD itself is an important genetically influenced risk factor for AD.

There is accumulating evidence from twin and adoption studies that genetic influences may account for a substantial proportion of the population variation in alcoholism risk (Heath, Slutske, & Madden, 1997), and recent evidence suggests that genetic influences may be as important for the development of

alcoholism in women as in men (Kendler, Heath, Neale, Kessler, & Eaves, 1992; Heath, Bucholz, et al., 1997). Relatively little is known about the mechanisms by which genes increase the risk for alcoholism.

One strategy for understanding the mechanisms by which genes contribute to the liability to develop alcoholism is to examine the extent to which common genetic influences account for an observed association between another trait, such as co-occurring psychiatric disorder, and alcoholism. In a population-based sample of over 1,000 female twin pairs, Kendler et al. (1995), using multivariate genetic and environmental structural equation modeling, showed that about 24% of the genetic variation in liability to alcoholism in women could be accounted for by genetic influences on major depression, bulimia, and the anxiety disorders (specific and social phobia, generalized anxiety, and panic disorder). This suggests that most of the genetic influences on alcoholism in women are not due to genetic influences associated with risk of depression, bulimia, and the anxiety disorders.

Rates of depression and the anxiety disorders are elevated in those with alcohol dependence (AD) compared with individuals without AD, but the strongest observed associations between AD and another non-substance-related psychiatric diagnosis are with antisocial personality disorder (ASPD) and with conduct disorder (CD; Helzer & Pryzbeck, 1988; Kessler et al., 1996; Regier et al., 1990). Although it has generally been assumed that antisocial behavior is not relevant to the etiology of AD in women (e.g., Cloninger, 1987), the association between antisociality and AD found in epidemiological surveys appears to be even stronger among women than among men (e.g., Helzer, Burnam, & McEvoy, 1991). Given the strong covariation between antisociality and alcoholism in both women and men, it is possible that genetic influences for CD or ASPD may also

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account for some of the genetic variation in AD liability in both sexes.

Results of family, adoption, and twin studies that have examined the familial association between childhood or adult antisocial behaviors and AD are equivocal. Most family studies that have examined this association, for example, by assessing rates of antisocial behaviors in the relatives of alcoholic adults or rates of alcoholism in the parents of children with CD, demonstrate significant familial cross-transmission between antisocial behaviors and AD (Amark, 1951; Lewis, Rice, & Helzer, 1983; Lynskey, Fergusson, & Horwood, 1994; Stewart, deBlois, & Cummings, 1980) but cannot resolve whether this is genetic or environmental in origin. Evidence from adoption studies suggests that the genetic transmission of antisocial behavior and AD are independent (Cloninger, Reich, & Guze, 1978; Cloninger & Reich, 1983), because a significant association between antisocial behavior in biological parents and AD in their adopted-away offspring or a significant association between AD in biological parents and antisocial behavior in their adopted-away offspring was not observed (Cadoret, O'Gorman, Troughton, & Heywood, 1985; Cadoret, Troughton, & O'Gorman, 1987; Cadoret, Yates, Troughton, Woodsworth, & Stewart, 1995; Crowe, 1974; Goodwin, Schulsinger, Hermansen, Guze, & Winokur, 1973; Schulsinger, 1972). The few twin studies that have addressed this issue, on the other hand, have found evidence to suggest common genetic influences for antisocial behaviors and AD. In a sample of twin pairs ascertained from alcohol and drug abuse treatment programs, McGue, Pickens, and Svikis (1992) found higher scores on a CD symptoms scale in male monozygotic (MZ) cotwins of alcoholics than in male dizygotic (DZ) cotwins of alcoholics, and Pickens, Svikis, McGue, and LaBuda (1995) found higher cross-trait cross-twin correlations between diagnosed AD in a twin and ASPD in the cotwin in male MZ versus DZ twin pairs. Grove et al. (1990), in a small sample of MZ twins reared apart, found substantial overlap between the genetic influences for alcohol problems and childhood conduct problems (genetic correlation of .54) and between alcohol problems and adult antisocial behaviors (genetic correlation of .75).

Interpretation of studies of the association between adult antisocial behavior and AD are complicated by the fact that alcohol use itself has been demonstrated to increase aggressiveness in experimental studies (Bushman & Cooper, 1990; Ito, Miller, & Pollock, 1996). Thus, determining whether ASPD and AD have common etiologies can be difficult because of the possible causal effect of alcohol on aggression. By studying the association between AD and antisocial behaviors that occur prior to substantial alcohol exposure, such as childhood CD, it may be possible to test the alternative hypotheses that CD causes AD or that CD and AD are caused by other common risk factors, such as genes.

Twin, family, and adoption studies have been consistent in demonstrating substantial familial aggregation for childhood antisocial behaviors but have been inconsistent concerning the relative role of genes and shared family environment in the familial aggregation. Whereas some studies have found evidence for substantial genetic influences in the development of childhood antisocial behavior problems (Eaves et al., 1997; Grove et al., 1990; Rowe, 1983; Slutske et al., 1997; Twito & Stewart, 1982), others have not (Lyons et al., 1995; see also Cloninger &

Gottesman, 1987; DiLalla & Gottesman, 1989). For example, in two recent twin studies of adult-reported childhood CD (the largest twin studies of CD to date), the estimates of the contribution of genetic factors to variation in risk for CD were 7% (Lyons et al., 1995) versus 43%–71% (Slutske et al., 1997).

In the present study, we examined the association between a history of childhood CD and lifetime history of AD in a large twin sample in which substantial genetic influences for CD have already been demonstrated (Slutske et al., 1997). We examined the extent to which genetic and environmental influences on the risk for CD can account for the genetic and environmental risk of developing AD and whether this differs for men and women.

Method

Participants

The participants were from the Australian National Health and Medical Research Council Twin Register (ATR), a volunteer twin panel recruited through the media, schools, and a variety of other sources (Jardine & Martin, 1984). Four alcohol-related studies have been carried out to date with the ATR sample: (a) a laboratory study of responses to alcohol conducted in 1978 and 1979 with a subset of the ATR sample (Heath & Martin, 1992; Martin, Oakeshott, et al., 1985; Martin, Perl, et al., 1985); (b) a questionnaire survey mailed to all members of the ATR in 1980 and 1981 (Heath, Madden, Slutske, & Martin, 1995; Jardine & Martin, 1984); (c) a follow-up questionnaire survey in 1988 and 1989, mailed to all twins from pairs in which both completed questionnaires for the previous survey (Heath, Cloninger, & Martin, 1994; Heath & Martin, 1994); and (d) a telephone interview survey conducted in 1992 and 1993 with individuals from the laboratory study and with twin pairs in which at least one twin participated in the 1988–1989 follow-up questionnaire survey targeted for interview (Heath, Bucholz, et al., 1994). Data obtained from the telephone interview survey were analyzed for the present study.

Responses were obtained from 8,183 individuals in the 1980–1981 survey, which represented a 69% individual response rate and from 6,327 individuals in the 1988–1989 survey, which represented a 83% individual response rate. Individual response rates in twin surveys are typically lower than those obtained from unrelated individuals in community surveys, because twin pairs are correlated for cooperativeness and often consult each other before choosing to participate. For example, the pairwise response rate (i.e., percentage of twin pairs in which both twins participated) in the 1980–1981 survey was 64%; if twin participation were uncorrelated, this would have yielded an individual response rate of 80%. The response rates obtained for this volunteer sample are similar to response rates obtained in other questionnaire surveys of community-based twin samples (e.g., Kendler et al., 1992; True et al., 1993).

Telephone interviews were completed with 5,889 individuals: 2,041 men (mean age = 42.7 years, range = 28–89) and 3,848 women (mean age = 44.8 years, range = 27–90).¹ After excluding twins who were deceased, had previously asked not to be contacted, were overseas, or could not be located, the cooperation rate for the telephone interview

¹ The reported sample size was 5,995 in some previous articles. Subsequently, we discovered that 106 individuals (36 twin pairs and 34 single twins) were interviewed who did not meet the criteria for inclusion in the 1992–1993 interview survey. The 106 participants had responded to mailed questionnaires of the ATR in 1980 or 1981, but had not participated (nor had their twins participated) in either the alcohol challenge study or the 1988–1989 mailed questionnaire survey. These 106 participants were excluded from the present study.

was 91% in men and 92% in women. There were 2,685 complete twin pairs. After excluding three pairs in which one twin's CD diagnostic data were incomplete, there were 2,682 twin pairs available for analysis (930 female MZ twin pairs, 396 male MZ twin pairs, 533 female-female DZ twin pairs, 231 male-male DZ twin pairs, and 592 female-male DZ twin pairs).

A number of checks were done to examine biases in the sample at each stage of assessment. Comparison with national norms, when available, provided a check on sampling bias. Yet another check on sampling bias exploited the longitudinal follow-up of the sample by comparing characteristics of those who were successfully followed up with those who were not. Twin data can provide additional information on possible sampling biases over and above that available for surveys of unrelated individuals. Given that twins are correlated for a trait, bias in the sample is reflected in differences between the cotwins of participating and nonparticipating individuals. Having twins report about their cotwins provides a more direct assessment of the characteristics of the nonparticipating cotwins of participants. Briefly, the most substantial and consistent biases in the sample were the over-representation of women and MZ twins, a characteristic of most volunteer twin samples, and the under-representation of the oldest twins because of infirmity or death. In addition, participants with higher educational attainments were over-represented. However, compared with a national survey of drinking practices, the alcohol use of the male participants was similar to that of the general population of Australia, whereas female heavier drinkers were over-represented (Jardine & Martin, 1984). Personality traits, as measured by the revised Eysenck Personality Questionnaire scales (Eysenck, Eysenck, & Barrett, 1985), did not appear to be strongly or consistently associated with study participation.

Further checks were carried out to determine the representativeness of the ATR with respect to CD and AD assessed at the telephone interview (Heath, Bucholz, et al., 1997; Slutske et al., 1997). If twins with CD or AD were less likely to be included in the sample, then a higher prevalence of these disorders would be observed in twins whose cotwins did not participate in the interview compared with the prevalence observed in twins whose cotwins did participate. The rates of CD and AD among the 519 twins whose cotwins did not participate in the interview did not differ significantly from the rates among the twins concordant for participation, which suggests that this sample is not biased with respect to CD and AD.

Nonetheless, concerns remained regarding the representativeness of the interviewed sample. Heath et al. (1996, 1998; Heath, Bucholz, et al., 1997) examined the impact of cooperation bias and attrition on rates of CD and AD and estimates of genetic and environmental influences on CD and AD liability by weighting the interview data to reflect (a) the distribution of educational attainment found in the general population of Australia, which was based on published national norms, and (b) the demographic and personality characteristics of all of the participants who took part in the first questionnaire survey in 1980 and 1981. The rates of CD and AD in the weighted data were very similar to the unweighted rates. Therefore, the over-representation of more highly educated respondents and sample attrition do not appear to have led to an under- or over-representation of individuals with CD or AD. Furthermore, twin correlations were nearly identical with the weighted and unweighted CD and AD data. The analyses of Heath et al. (1996, 1998; Heath, Bucholz, et al., 1997) suggest that sampling bias should not have substantially affected the results of this study. One possible exception, however, is that severe cases of CD or AD, or those with co-occurring CD and AD, may have been under-represented in this community-based sample, a possibility that is quite likely but difficult to assess. If severe CD or AD or co-occurring CD and AD are etiologically distinct from less severe CD or AD, this may have affected the results of the present study.

Measures

Zygosity. Twin zygosity diagnoses were mainly based on questionnaire responses concerning physical similarity and how often the twins were mistaken for each other as children. This method of zygosity diagnosis has been shown to be about 95% accurate, as validated against blood typing (Eaves, Eysenck, & Martin, 1989). In addition, however, pairs in which the zygosity was ambiguous or in which there was disagreement between cotwins were followed-up for further information, and in many cases twins were asked to provide photographs to assist in assigning zygosity. There was perfect agreement between the final zygosity diagnoses and the zygosity assignment based on eight DNA microsatellite markers in 190 same-sex twin pairs from the present study (Duffy, 1994).

Conduct disorder. The Semi-Structured Assessment for the Genetics of Alcoholism interview (SSAGA; Bucholz et al., 1994), originally developed for the Collaborative Study on the Genetics of Alcoholism (COGA), was modified for use as a telephone interview in Australia. Interviews were administered by trained lay interviewers who were unaware of the psychiatric status of the cotwin. Interviewers were supervised by a project coordinator, a qualified clinical psychologist with 4 years of experience. All interview protocols were reviewed either by the project coordinator or by the most skilled interviewers (those who maintained consistently low error rates in coding); the reviews were always done by someone other than the person who conducted the interview. In addition, all interviews were tape-recorded, and a random sample of interview tapes were reviewed for quality control and coding inconsistencies.

Individual CD symptoms were assessed by telephone interview with the modified SSAGA. The individual CD symptoms were aggregated into a lifetime CD diagnosis by a computer algorithm. Two definitions of CD, corresponding to the definition of CD in the *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed., rev.; *DSM-III-R*; American Psychiatric Association, 1987; endorsement of three or more CD symptoms occurring at any time prior to age 18) and to the childhood criterion for *DSM-III-R* antisocial personality disorder (endorsement of three or more CD symptoms occurring at any time prior to age 15), were used in the present study. The rates of these two definitions of CD in this sample were 18% and 13%, respectively, in men and 3% and 2%, respectively, in women (Slutske et al., 1997). Unless specified, analyses were conducted with the broader definition of CD because of increased statistical power, and analyses using the narrower definition of CD were conducted to rule out possible causal and noncausal explanations for the association between CD and AD.

The 1-week interrater test-retest reliability of narrow CD, assessed by the SSAGA interview, was .64-.65 indexed by Yule's *Y* (Spitznagel & Helzer, 1985) and was .80-.82 indexed by the tetrachoric correlation (unpublished data from Bucholz et al., 1994). Stability of retrospective reports of childhood CD was examined in 604 participants from the present study who were reinterviewed (by telephone or personal interview) an average of 15 months later (range = 2-24 months). The stability of narrow CD, as indexed by Yule's *Y* and the tetrachoric correlation, was .76 and .83, respectively, and was .67 and .78, respectively, for broad CD (Slutske et al., 1997). The 15-month stability of the retrospective reports of childhood CD assessed in these adult participants was as high as the short-term reliabilities obtained for the SSAGA interview.

Alcohol dependence. Individual AD symptoms were assessed by telephone interview and aggregated into lifetime *DSM-III-R* diagnoses by computer algorithm. In this sample, the *DSM-III-R* definition yielded AD rates of 24% in men and 6% in women (Heath, Bucholz, et al., 1997). The 1-week interrater test-retest reliability of AD assessed by the original SSAGA interview was .87-.90 indexed by Yule's *Y* (Bucholz et al., 1994). Tetrachoric correlations for this same definition of AD were .97-.99 (unpublished data from Bucholz et al., 1994).

Heath, Bucholz, et al. (1997) obtained a tetrachoric correlation of .77 between independent interview assessments of AD conducted, on average, 1–3 years apart with 1,117 female twins from the present study. The reliability of lifetime diagnoses of AD is very high and exceeds that of most other psychiatric diagnoses (Slutske et al., 1998).

For each symptom of AD endorsed, the age of onset of the symptom was obtained. The age of onset of AD, for the purposes of this study, was defined as the age at which the participant first had symptoms from three or more *DSM-III-R* symptom groups (i.e., the first age that the participant could have met the diagnostic criteria for AD). Participants were also asked the age at which they first drank at least once a month for 6 months or more, the age at which they first got drunk, and whether they had gotten drunk more than once before the age of 15. Although retrospective reports of the lifetime occurrence of psychiatric symptoms can be obtained with good reliability, the age of onset of occurrence is not reported with as high a reliability. Retrospectively reported ages of onset in the present study should be interpreted with caution.

Data Analysis

In univariate model fitting of twin data, the variation in liability for a single trait is partitioned into that due to additive genetic influences (A), shared environmental influences (C), and nonshared environmental influences and measurement error (E). In bivariate model fitting of twin data, this is done for each of two traits, and in addition, the correlation between the two traits is similarly decomposed into that portion that is due to additive genetic influences, shared environmental influences, and nonshared environmental influences (and measurement error that is correlated in the two traits).

For each of the five Sex \times Zygosity groups, a 4×4 matrix of tetrachoric correlations was generated by the method of maximum likelihood using PRELIS (Jöreskog & Sörbom, 1988). The tetrachoric correlation (Olsson, 1979), or correlation in liability, is used when one assumes that scores on the observed ordinal variables can be explained by underlying, normally distributed latent variables. For the present study, we assumed that there were normally distributed continua of liability underlying the categorical diagnoses of CD and AD (Falconer, 1965; Gottesman & Shields, 1967; Reich, Cloninger, & Guze, 1975). This assumption has been tested for CD (Slutske et al., 1997) and AD (Kendler et al., 1992), and in neither case could it be rejected.

Two elements of the matrices of tetrachoric correlations were the *within-trait cross-twin correlations* for CD and AD. Bivariate analyses require four additional correlations: (a) two *cross-trait within-twin correlations* between CD and AD for each twin from a pair in twins randomly designated as the first and second twins and (b) two *cross-trait cross-twin correlations* between CD and AD, first of CD status in the first twin with AD status in the second twin and then of AD status in the first twin with CD status in the second twin.

When twin data for a single trait are analyzed, the within-trait cross-twin correlations are compared in MZ and DZ twins. When data are collected for two or more traits, one can make similar inferences about the source of the correlation between traits by comparing the cross-trait cross-twin correlations in MZ and DZ twins in relation to the cross-trait within-twin correlation between the two traits. Thus, if the MZ cross-trait cross-twin correlation between CD and AD is nearly as large as the cross-trait within-twin correlation between CD and AD, this would suggest that there are important familial factors (either genetic or environmental) that are causing the correlation between the traits. The magnitude of the DZ relative to the MZ cross-trait cross-twin correlation determines the relative importance of genetic versus shared environmental factors in explaining the correlation between the traits. If the DZ cross-trait cross-twin correlation between CD and AD is lower than the MZ cross-trait cross-twin correlation, this would suggest that genetic influences (at least partially) explain the correlation between CD and

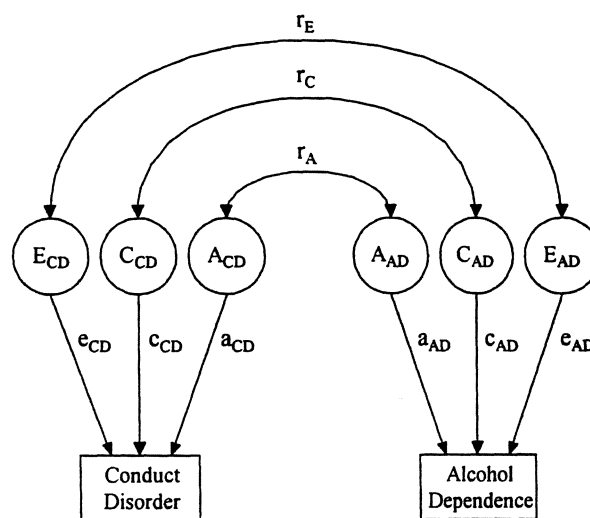


Figure 1. Path diagram of the association between conduct disorder (CD) and alcohol dependence (AD) for a single individual. The variance in liability for CD and AD is decomposed into that due to the effects of additive genetic influences (A), shared environmental influences (C), and nonshared environmental influences, including measurement error (E). The paths with single arrows (a , c , and e) from the latent genetic, shared environmental, and nonshared environmental effects to the traits of CD and AD, when squared, yield the proportion of variation in liability to CD and AD attributable to that source. The correlation between CD and AD liability is similarly decomposed into that due to additive genetic influences (r_A), shared environmental influences (r_C), and nonshared environmental influences (r_E).

AD. Conversely, if the DZ cross-trait cross-twin correlation between CD and AD is nearly as large as the MZ cross-trait cross-twin correlation, then shared environmental factors may be important in causing the correlation between CD and AD. (For further explanation of multivariate genetic analysis, see Carey & DiLalla, 1994.)

Genetic and environmental models were fitted to the five twin correlation matrices and to the corresponding asymptotic covariance weight matrices by the method of weighted least squares, using the Mx program (Neale, 1995). The fit of a series of nested submodels was compared by likelihood-ratio chi-square to the most general full model, illustrated for a single individual in Figure 1, which allowed for additive genetic, shared environmental, and nonshared environmental factors as sources of variation for and covariation between the liability to CD and AD. For example, models in which the genetic influences were fixed at 0 were compared with the model containing all three sources of variation. When dropping parameters from a model did not result in a statistically significant decrement in model fit (i.e., there was a nonsignificant likelihood-ratio chi-square test), then the reduced model was considered to give a better (i.e., more parsimonious) fit to the data. The following questions were evaluated using the likelihood-ratio chi-square test: (a) whether the parameter estimates from the model illustrated in Figure 1 were significantly different for men and women, (b) whether the magnitude of genetic (or shared environmental) influences for CD and AD (i.e., paths a_{CD} and a_{AD} or c_{CD} and c_{AD} from Figure 1) differed significantly from 0, (c) whether the genetic or environmental correlations between CD and AD (i.e., paths r_A , r_C , or r_E from Figure 1) differed significantly from 0, and (d) whether the genetic or environmental correlations between CD and AD differed significantly from 1. Selected as the final best-fitting model was the simplest model that was consistent with the

data (see Heath, Neale, Hewitt, Eaves, & Fulker, 1989; Neale & Cardon, 1992, for further details about model fitting).

The overall adequacy of the fit of a particular model to the data was assessed by the goodness-of-fit chi-square test. Unlike most significance testing in psychological research, the goal is to obtain a nonsignificant goodness-of-fit chi-square; this indicates that the model cannot be rejected because it provides an adequate explanation of the covariance structure in the data.

Results

Association Between CD and AD

There was a strong association between CD and a lifetime history of AD in both men (tetrachoric $r = .34$, $p < .001$) and women (tetrachoric $r = .53$, $p < .001$).² The rate of AD in men with CD was 41%, compared with a rate of 20% in men without a history of CD (odds ratio = 2.8, $p < .001$), and the rate of AD in women with CD was 34%, compared with a rate of 5% in women without a history of CD (odds ratio = 9.9, $p < .001$). The associations were equally strong between narrow CD and AD (men: $r = .35$, odds ratio = 3.0, $p < .001$; women: $r = .47$, odds ratio = 8.3, $p < .001$).

Subsyndromal levels of CD symptoms were also associated with AD; in women, a single symptom of CD was associated with a significant increase in the rate of AD, and in men, two symptoms significantly increased the rate of AD. Although only a minority of men and women in the sample had diagnosable CD (18% and 3%, respectively), many more had enough CD symptoms to significantly increase their risk of AD (33% and 29%, respectively).

Temporal Sequence of CD and AD Onset

The median retrospectively reported age of onset of AD was 18 years in both men and women (men: $M = 18.2$, $SD = 3.0$, range = 10–35; women: $M = 20.9$, $SD = 6.8$, range = 10–56).³ Ages of onset of CD were not obtained, so it was not possible to determine the number of individuals who exhibited CD prior to the onset of AD and the number who had AD prior to the onset of CD. However, we could identify individuals whose CD onset most likely preceded their AD onset because they met diagnostic criteria for CD but not AD prior to age 18 or because they met criteria for CD but not AD prior to age 15. As many as 55% of the men and 52% of the women with both disorders *could* have had an AD onset prior to the onset of broad CD. When examining the association between broadly defined CD and AD, it is unclear whether some of the CD behaviors may have occurred while the individual was under the influence of alcohol. Thus, it is possible that the association between CD and AD was in part spurious (i.e., the same behavior sometimes contributed to symptoms for both diagnoses) or that AD was causing CD in many cases.

Nevertheless, in the majority of individuals with both CD before age 15 and AD, the onset of AD followed the onset of CD; 88% of men and 81% of women with both disorders had an AD onset after age 15. In addition, most participants with this definition of CD had only minimal exposure to alcohol before age 15. The association between CD before age 15 and AD is unlikely to have been spurious or due to the causal influ-

ence of AD (or heavy alcohol use) on CD. Thus, comparing the results of the association between CD and AD for the two definitions of CD (with an onset prior to age 18 and prior to age 15) should help to sort through various causal interpretations.

Cross-Twin Correlations Between CD and AD

Cross-twin correlations between CD and AD are presented in Table 1. For men, the within-twin correlation between CD and AD was .38 among MZ twins and .33 among same-sex DZ twins; the correlation between CD in a twin and AD in his co-twin was .29 for MZ twin pairs, and only .05 for DZ twin pairs (.29 vs. .05), $\chi^2(1) = 4.63$, $p = .03$. The high MZ and low DZ cross-twin correlations relative to the magnitude of the within-twin correlation suggested that the co-occurrence between CD and AD, at least in men, was mostly genetically mediated. In women, there was a large within-twin correlation of .52 among MZ twins and .59 among same-sex DZ twins between CD and AD, but there were nearly equal cross-trait cross-twin correlations of .35 and .27 for MZ and DZ twin pairs, respectively, $\chi^2(1) = 0.31$, $p = .58$. This pattern suggested that environmental factors, both shared and not shared by members of a twin pair, may be important in the covariation between CD and AD in women. The different patterns observed in male and female twin pairs suggest that the sources of co-occurrence of CD and AD in men and women may differ. The correlations for narrow CD were similar to those presented in Table 1 for CD with an onset before age 18.

Examining the unlike-sex DZ cross-twin correlation provides a test of the hypothesis of sex differences in the sources of covariation between CD and AD. If the causes of covariation between CD and AD differ in men and women, then the unlike-sex DZ cross-trait cross-twin correlation should be lower than the cross-trait cross-twin correlations found in same-sex DZ twin pairs. The DZ unlike-sex cross-trait cross-twin correlation of .13 was in between the values of .05 and .27 observed in same-sex DZ male and female pairs, respectively, and suggested that the causes of covariation between CD and AD may not differ substantially in men and women. Rigorous model-fitting methods, which simultaneously consider and correctly weight all of the information in the data, tested whether the pattern of correlations for same-sex male, same-sex female, and unlike-sex twin pairs was consistent with the hypothesis of sex differences in the sources of covariation between CD and AD.

² Individuals within twin pairs were treated as individual participants in the analyses of the association between CD and AD. Parameter estimates (e.g., correlations, odds ratios) are unbiased in such analyses, but because observations from twins are not independent, the sampling variance of parameter estimates are underestimated; therefore, Type I error rates may be inflated. In the *Association Between CD and AD* section, a conservative approach was used to correct for this potential bias by dividing the original sample size by 2 to approximate the number of independent observations. The p values associated with this more conservative approach are also presented in this section.

³ Kessler et al. (1997), using a similar method to diagnose and calculate the age of onset of *DSM-III-R* AD, also obtained a median age of onset of 18 years in a general population survey in the U.S.

Table 1
Within-Trait and Cross-Trait Tetrachoric Correlations for Childhood Conduct Disorder (CD) and Alcohol Dependence (AD) in Australian Male and Female Twins

Zygosity group	n pairs	Within trait				Cross trait ^a			
		CD		AD		Within twin		Cross twin	
		r	SE	r	SE	r	SE	r	SE
MZ male	396	.70	.06	.68	.06	.38	.06	.29	.07
DZ male	231	.37	.12	.20	.12	.33	.08	.05	.09
MZ female	930	.68	.10	.58	.08	.52	.08	.35	.10
DZ female	533	.48	.16	.29	.14	.59	.08	.27	.12
DZ unlike sex	592	.34	.12	.43	.09	.35 ^b	.07	.13	.08
						.48 ^c	.13		

Note. MZ = monozygotic; DZ = dizygotic.

^a Except for the within-twin correlations in DZ unlike-sex pairs, the within-twin tetrachoric correlations and cross-twin correlations for first and second twins (i.e., of CD status in the first twin with AD status in the second twin and of AD status in the first twin with CD status in the second twin) were pooled together to simplify presentation, because none of the correlations for first and second twins were significantly heterogeneous. ^b Men. ^c Women.

Bivariate Model Fitting of the Association Between CD and AD

The results of bivariate model fitting of the association between CD and AD are presented in Table 2. The parameter estimates from a full model are shown in Figure 2. The paths with single arrows from the latent genetic effects and nonshared environmental effects to the traits of CD and AD, when squared, yield the proportion of variation in liability to CD and AD attributable to that source. Therefore, according to this model, additive genetic influences accounted for 56%–74%, shared environmental influences accounted for 0%–12%, and nonshared environmental influences accounted for 26%–37% of the variation in CD and AD liability in men and women. The correlation between genetic risk factors for CD and AD was .59 in men and .71 in women, the correlation between shared environmental risk factors for CD and AD in both men and women was –1.0, and the correlation between nonshared environmental risk factors for CD and AD was .26 in men and .46 in women. Because shared environmental influences contributed only a small portion of the variation in liability to CD and AD, the perfect negative correlation between these risk factors is not particularly meaningful and so should not be accorded theoretical significance.⁴ The full model fit the data well: goodness-of-fit $\chi^2(16) = 18.21, p = .31$.⁵

The hypothesis of no sex differences in the parameter estimates was not rejected (Model 2 vs. 1 in Table 2). The hypothesis of no shared environmental influences also could not be rejected (Model 3 vs. 2), but the hypothesis of no genetic influences was rejected (Model 4 vs. 2). A model that included genetic and nonshared environmental influences as sources of variation and covariation for CD and AD liability was used as a base model against which to test hypotheses about the genetic and nonshared environmental correlations between the liability to CD and AD. The hypothesis that the genetic correlation between CD and AD was zero was rejected (Model 5 vs. 3), as was the hypothesis that the genetic risk factors for CD and AD

were perfectly correlated (Model 6 vs. 3). Similar hypotheses concerning the nonshared environmental correlation between CD and AD liability were also rejected (Models 7 and 8 vs. 3).

The model fitting had thus far indicated that Model 3 in Table 2 provided the best fit to the data. This model suggested that there were no sex differences in the sources of variation for and covariation between CD and AD liability and that the genetic correlation between CD and AD was significantly greater than 0 and significantly less than 1. When the model fitting was repeated for CD with an onset prior to 15, the same result was obtained.

Sex Differences in the Causes of Covariation Between CD and AD

For both definitions of CD used in the present study, the magnitude of the association with AD was significantly greater in women than in men, and some of the descriptive data presented in Table 1 suggested that the mechanisms explaining the covariation between CD and AD may differ in men and women. However, there was no evidence for sex differences in the causes of variation in and covariation between CD and AD in the

⁴ When the same full model was fit to the data on narrow CD and AD, the estimated correlation between shared environmental risk factors for the two disorders was large but *positive* in both men ($r_c = .88$) and women ($r_c = .96$).

⁵ The effect of birth cohort (higher rates of CD and AD in those more recently born) accounted for a significant portion of the variation in CD and AD risk and the covariation between the disorders. Birth cohort accounted for 2% and 6% of the variation in CD risk and accounted for 2% and 5% of the variation in AD risk in men and women, respectively. Of the association between CD and AD, 5% in men and 10% in women was accounted for by birth cohort effects. Because the estimates of other parameters were not substantially altered when the effect of birth cohort was excluded, we present models without birth cohort effects to simplify presentation.

Table 2

Bivariate Model-Fitting Results for Conduct Disorder and Alcohol Dependence

Model	Goodness-of-fit test			Models compared	Likelihood-ratio test		
	χ^2	<i>df</i>	<i>p</i>		χ^2	<i>df</i>	<i>p</i>
1. Full model, ACE, all sex-specific par.	18.21	16	.31				
2. ACE, no sex-specific par.	30.64	23	.13	2 vs. 1	12.43	7	.09
3. AE, no sex-specific par.	30.91	26	.23	3 vs. 2	0.27	3	.97
4. CE, no sex-specific par.	62.12	26	<.001	4 vs. 2	31.28	3	<.001
5. AE, no sex-specific par., $r_A = 0$	86.18	27	<.001	5 vs. 3	55.27	1	<.001
6. AE, no sex-specific par., $r_A = 1$	84.55	27	<.001	6 vs. 3	53.64	1	<.001
7. AE, no sex-specific par., $r_E = 0$	38.74	27	.07	7 vs. 3	7.83	1	.005
8. AE, no sex-specific par., $r_E = 1$	50.08	27	.004	8 vs. 3	19.17	1	<.001
9. AE, all sex-specific par.	20.01	22	.58	9 vs. 3	10.90	4	.03
10. Best-fitting model, AE, sex-specific r_A and r_E	20.23	24	.68	10 vs. 9	0.22	2	.90
11. AE, sex-specific r_A	21.21	25	.68	11 vs. 10	0.98	1	.32
12. AE, sex-specific r_E	22.40	25	.61	12 vs. 10	2.17	1	.14

Note. A = additive genetic effects; C = shared environmental effects; E = nonshared environmental effects; par. = parameters; r_A = the correlation between additive genetic effects for conduct disorder and alcohol dependence liability; r_E = the correlation between nonshared environmental effects for conduct disorder and alcohol dependence liability.

bivariate model-fitting analyses presented above. Nonetheless, sex-specific models of the association between CD and AD were examined further for several reasons. First, the question of sex differences was of particular interest. Second, the likelihood-ratio chi-square test comparing the adequacy of a model that equated parameters in men and women to a sex-limitation model approached statistical significance ($p = .09$; see Table 2). Third, failure to find evidence for sex differences may have been due to a lack of statistical power.

Model fitting was repeated, this time allowing sex differences to remain while testing whether additive genetic and shared environmental parameters were necessary to account for the covariance structure for each sex. In both men and women, shared environmental influences, but not additive genetic influences, could be dropped from the model without a significant decrement in the model fit (Model 9 in Table 2). The relative contribution of additive genetic and nonshared environmental influences as sources of variation for CD and AD were very similar in men and women, but the genetic and environmental correlations between CD and AD were larger in women than in men. When this model was compared with a model that equated all parameters in the model across the sexes, there was then a significant deterioration in model fit (Model 9 vs. 3). Thus, this alternative approach to selecting a model suggested that there were important sex differences in the sources of variation for or covariation between liability to CD and AD.

Further model fitting suggested that the sources of variation for CD and AD did not differ in men and women (Model 10 vs. 9) and that either the nonshared environmental correlation (Model 11 vs. 10) or the genetic correlation (Model 12 vs. 10) but not both (Model 3 vs. 10), likelihood-ratio $\chi^2(2) = 10.68$, $p = .005$, could be equated in men and women without a significant deterioration in model fit. Because of the similarity in the fit of Models 11 and 12, it was not possible to resolve whether the larger correlation between CD and AD in women than in men was due to correlated genetic or nonshared environmental factors; therefore, Model 10 in Table 2 was judged the best-fitting model in terms of fit, parsimony, and lack of arbitrariness. Parameter estimates from this model are shown in Figure 3. According to this model, additive genetic influences in both men and women accounted for 73% and 66%, respectively, and nonshared environmental influences accounted for 27% and 34%, respectively, of the variation in CD and AD liability. The correlation between genetic risk factors for CD and AD was .41 (95% confidence interval [CI] = .27–.56) in men and .59 (95% CI = .40–.78) in women, and the correlation between nonshared

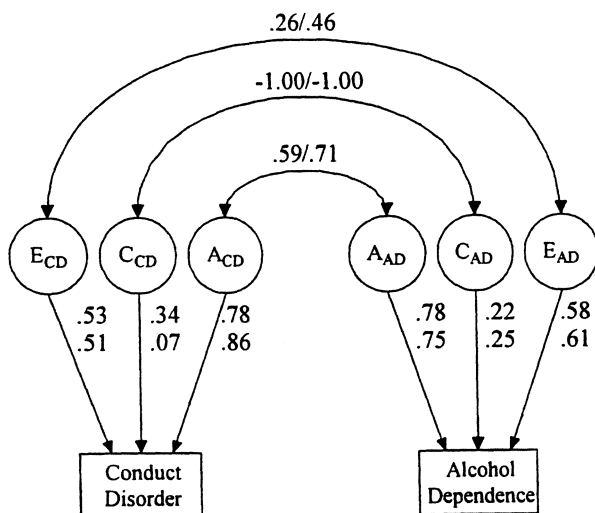


Figure 2. Parameter estimates from a full model of the association between conduct disorder (CD) and alcohol dependence (AD). The paths with single arrows from the latent genetic effects (A), shared environmental effects (C), and nonshared environmental effects (E) to the traits of CD and AD, when squared, yield the proportion of variation in liability to CD and AD attributable to that source. Parameter estimates for men are given on the left or top, and parameter estimates for women are given on the right or bottom.

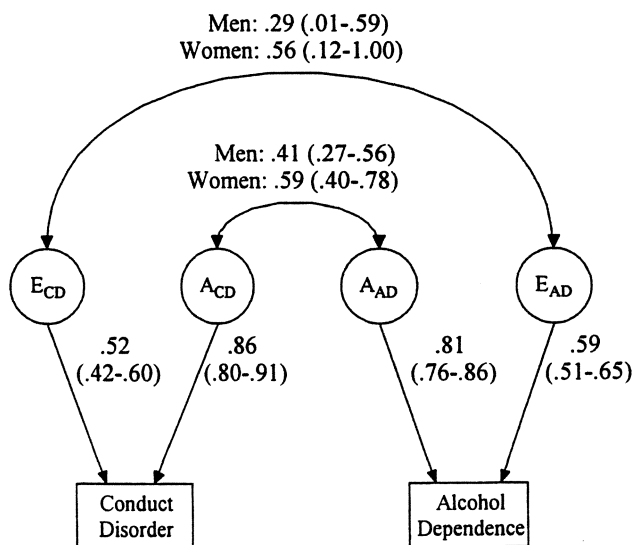


Figure 3. Best-fitting model of the association between conduct disorder (CD) and alcohol dependence (AD). Parameter estimates for men and women did not significantly differ unless separate estimates are provided. The 95% confidence intervals around parameter estimates are in parentheses. Path coefficients (and upper and lower confidence limits) can be squared to yield the proportion of variation in liability to CD and AD attributable to genetic (A) and environmental (E) factors.

environmental risk factors for CD and AD was .29 (95% CI = .01-.59) in men and .56 (95% CI = .12-1.00) in women. As can be seen from the 95% CIs, when the genetic and environmental correlations were allowed to vary for men and women, the hypothesis that the nonshared environmental factors contributing to CD and AD liability are perfectly correlated could not be rejected in women but could be rejected in men. When the same model fitting was conducted to examine possible sex differences in the sources of variation in and covariation between narrow CD and AD, there was still no evidence for sex differences.

Discussion

The causes of covariation between CD and AD were examined in a large community-based sample of adult Australian twins. The results were consistent with earlier reports using the same sample (Heath, Bucholz, et al., 1997; Slutske et al., 1997) that suggested that the variation in liability to both CD and AD was best accounted for by additive genetic and nonshared environmental effects, and that the magnitude of these effects among women did not significantly differ from their effects among men. The results of the present study further suggested that the substantial covariation between CD and AD in both men and women was largely due to the influence of genes that increase the risk for both disorders. In the best-fitting model, 76% and 71% of the phenotypic association between CD and AD, in men and women respectively, was due to genes that are common risk factors for the two disorders. The remaining 24% and 29% of the association in men and women was due to nonshared, or individual-specific, environmental risk factors

common to CD and AD risk. Genetic influences common to CD and AD liability accounted for 17% and 35% of the genetic variation in liability to *DSM-III-R* AD in men and women, respectively, and accounted for 11% and 23% of the total variation in AD liability in men and women, respectively. The results of this study suggest that CD and AD are not etiologically or genetically distinct disorders—they share common genetic risk factors that account for most of the observed association between the disorders. The magnitude of the genetic correlation between CD and AD liability was at least as high among women as among men.

The results of the present study are broadly consistent with the results of several twin studies that have examined the causes of covariation between antisocial behavior disorders and AD, but at first our results appear to contradict the findings of adoption studies that have concluded that antisocial behavior disorders and AD are etiologically distinct. The reason for the discrepancy between findings from the adoption and twin studies may be that twin studies are more powerful than adoption studies for detecting genetic covariation between traits (Carey & DiLalla, 1994). The power to detect cross-transmission (i.e., a significant association between one trait in an individual and another trait in a relative) is usually weaker than the power to detect familial transmission for a single trait. Power is further reduced when dyads of relatives are not very closely related genetically. In adoption studies, one examines genetic cross-transmission between first degree relatives, who share an average of one half of their genes. In many cases, especially when sample sizes are not particularly large, there may be insufficient power to detect an important genetic association between two traits in first degree relatives. Twin studies have added power for investigating the genetic covariation between traits because of the inclusion of MZ twins, who are genetically identical (Carey & DiLalla, 1994).

Another advantage of twin studies over adoption and family study designs for examining the genetic covariation between traits is that statistical power may be greater when relatives belong to the same generation or birth cohort (e.g., twins or siblings) compared with relatives belonging to different birth cohorts (e.g., parent and offspring), because there may be secular trends for a disorder, such that different genes are relevant for a trait in different generations. The discrepancy between the twin and adoption studies examining the cotransmission of antisociality and AD is most likely due to differences in statistical power in the study designs.

Other studies (e.g., Lyons et al., 1995) have not found evidence of significant genetic influences for symptoms of CD and thus cast some doubt on the replicability of these results. Follow-up analyses of the association between CD and AD in the Vietnam era twin sample of Lyons et al. (1995) yielded substantial genetic and shared environmental correlations between CD and AD, but because of the imprecision of the estimates of the correlations, the source of the coaggregation of CD and AD (i.e., to what extent it was due to genes or family environment) was not resolvable (True et al., 1997). Consistent across the present study, the study of True et al. (1997), and a recent family study by Stallings et al. (1997) is the conclusion that familial factors are primarily responsible for the substantial correlation between CD and AD. Additional research may help to clarify

the role of genes in the etiology of CD and resolve the inconsistencies in the literature.

Limitations

The present study should be interpreted in light of two main limitations that may have affected the results. First, the sample used was a volunteer twin register, which likely under-represents those with a history of severe or persisting antisocial behavior. Although it is reasonable to assume that those with CD or ASPD may be more difficult to recruit into psychiatric surveys, studies of more systematically ascertained samples suggest that it may actually be those without symptomatology who are hesitant to participate (Bucholz et al., 1996) and that those with ASPD are not particularly uncooperative (Bucholz et al., 1996; Cottler, Zipp, Robins, & Spitznagel, 1987). Without systematic ascertainment or suitable population norms, it is difficult to know the extent to which those with antisocial traits were under-represented in the ATR. Nonetheless, with the data that were available, we were able to find little evidence of bias in the sample.

The other main limitation is that the data were cross-sectional, and both CD and AD diagnoses were based on retrospective reports. Although we have demonstrated adequate reliability of the diagnoses, biases in retrospective accounts still may have inflated the observed association between CD and AD in the present study or may have inflated the extent to which the association was due to genetic or environmental factors. For example, the significant nonshared environmental correlation between CD and AD may have been due to correlated error of measurement induced by assessing both disorders at the same time. The advantage of the retrospective method used in the present cross-sectional study is that the association between CD and AD could be examined in a sample that is nearly through the age period of risk for both disorders. It will be important to attempt to replicate this study using prospective twin data.

Implications

The size of a genetic correlation does not have a straightforward interpretation at the molecular genetic level; it is not a good indicator of the number or proportion of susceptibility loci that the disorders have in common (Carey, 1988). The results of the present study are consistent with the view that there is at least one genetic locus that increases the risk for both CD and AD or that CD is a genetically influenced risk factor for AD. The former interpretation is supported by recent research in which a specific genotype was associated with both increased alcohol consumption and aggressive behavior in mice (Crabbe et al., 1996).

Future research should be aimed at identifying those genetically influenced risk factors that contribute to the development of both CD and AD. Many of the personality correlates of AD are also correlates of ASPD (Sher & Trull, 1994). For example, several personality dimensions that are correlated with a history of AD in adults (McGue, Slutske, Taylor, & Iacono, 1997)—aggression, social alienation, and impulsivity—are also correlated with a history of CD and delinquency in adolescents (Krueger et al., 1994; Krueger, Caspi, Moffitt, Silva, & McGee, 1996). In addition, the verbal-language-skills deficits found in

delinquent youth (Moffitt, 1993) are also found in young adults at risk for AD (Drejer, Theilgaard, Teasdale, Schulsinger, & Goodwin, 1985; Sher, Walitzer, Wood, & Brent, 1991).

Although the correlation between CD and AD was mostly due to genetic factors, there was also a significant correlation between the individual-specific environmental risk factors for CD and AD. In fact, the hypothesis that the nonshared environmental risk factors for the two disorders were perfectly correlated in women could not be rejected. Common nonshared environmental risk factors for CD and AD could be any characteristic or experience unique to an individual, that is, those not shared by a twin and her cotwin, such as different peer groups, school experiences, treatment by parents, and stressful or traumatic life events (see Rodgers, Rowe, & Li, 1994).

The temporal association between CD and AD suggests that CD may be an important pathway through which the common genetic liability for CD and AD increases the risk for the development of AD. Cross-sectional epidemiological surveys (e.g., Kessler et al., 1996) have shown that the onset of CD usually precedes the onset of AD, and longitudinal studies have confirmed this temporal association (Robins, Bates, & O'Neal, 1962; Vaillant & Milofsky, 1982; Zucker & Gombert, 1986). The within-twin and familial associations between CD and AD in the present study were similar regardless of whether the age-of-onset criterion for CD was less than 18 or less than 15 years, and there was minimal temporal overlap in CD with an onset prior to age 15 and the onset of AD (or heavy alcohol use). Therefore, the hypothesis that CD causes AD is more plausible than the hypothesis that AD causes CD or that the association between CD and AD is spurious. Of course, temporal ordering is a necessary but not sufficient condition for inferring that CD causes AD. Under certain restricted circumstances, for example, when one trait is largely influenced by genetic factors and the other is largely influenced by family environmental factors, structural equation models fitted to twin and family data can provide information about the direction of causation of the association between two traits (Carey & DiLalla, 1994; Duffy & Martin, 1994; Heath et al., 1993; Neale & Kendler, 1995). With data from the present study, these models were not able to resolve the direction of causation of the association between CD and AD. The observed correlations were nearly as consistent with the hypothesis that AD causes CD as with the hypothesis that CD causes AD.

A promising area of future research would be to determine more precisely the mechanisms by which CD itself may act as a risk factor for AD. It is clear that CD increases the probability of alcohol and drug use (Boyle et al., 1993; Lynskey & Fergusson, 1995; Robins & McEvoy, 1990; Windle, 1990) and decreases the age at which alcohol and drugs are first used (Robins & McEvoy, 1990). Thus, it appears that youth with CD may be at greater risk for AD because of increased and earlier exposure to alcohol. In addition, however, CD confers increased risk for the progression to substance abuse even after controlling for exposure and the timing of exposure (Robins & McEvoy, 1990), and CD also contributes to the maintenance of alcohol abuse among those already evidencing problems (Myers, Brown, & Mott, 1995). Antisocial behavior disorders may play an important role in the many stages of the development of AD, from the initiation of alcohol use to the progression from regular

drinking to heavy drinking, and in the maintenance and progression of alcohol-related problems. The mechanisms by which this occurs largely remain to be determined.

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