Background: Little is known about genetic factors that underlie the interrelationships among antisocial personality disorder (ASPD), major depression (MD), alcohol dependence (AD), and marijuana dependence (MJD). We examined the contribution of genetic effects associated with ASPD to the comorbidity of MD and substance use disorders.

Methods: The Vietnam Era Twin Registry is a general population registry of male veteran twins constructed from computerized Department of Defense files and other sources. A telephone diagnostic interview was administered to eligible twins from the Registry in 1992. Of 5150 twin pairs who served on active military duty during the Vietnam era, 3360 pairs (1868 monozygotic and 1492 dizygotic) in which both members completed the pertinent diagnostic interview sections were included. The main outcome measures were lifetime DSM-III-R ASPD, MD, AD, and MJD.

Results: Structural equation modeling was performed to estimate additive genetic, shared environmental, and nonshared environmental effects common and specific to each disorder. The heritability estimates for lifetime ASPD, MD, AD, and MJD were 69%, 40%, 56%, and 50%, respectively. Genetic effects on ASPD accounted for 38%, 50%, and 58% of the total genetic variance in risk for MD, AD, and MJD, respectively. After controlling for genetic effects on ASPD, the partial genetic correlations of MD with AD and with MJD were no longer statistically significant. Genetic effects specific to MD and AD and familial effects specific to MJD remained statistically significant. Nonshared environmental contributions to the comorbidity in these disorders were small.

Conclusions: In this sample, the shared genetic risk between MD and both AD and MJD was largely explained by genetic effects on ASPD, which in turn was associated with increased risk of each of the other disorders.

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served significant genetic correlations between MD and AD. The extent to which genetic vs shared environmental factors contribute to the comorbidity of conduct disorder (or ASPD) and AD has been more controversial. Common genetic risk factors have been suggested to account for 76% and 71% of the phenotypic association between conduct disorder and AD in Australian male and female twins, respectively.34 Shared environmental risk factors were found to be responsible for comorbid conduct disorder and alcohol use disorder in the Vietnam Era Twin (VET) Registry.32 A study32 of monozygotic (MZ) twins reared apart reported a high genetic correlation (r = 0.75) between DSM-III ASPD and AD symptom counts, whereas another study67 of twins reared together found a common genetic vulnerability between DSM-III ASPD and AD in men but an overlap between shared environmental risk factors for ASPD and AD in women.

Family and twin studies have also been used to examine the co-transmission of ASPD and marijuana use disorder. In a recent family study68 of substance use disorder, no familial coaggregation of ASPD and cannabis use disorder was found, but the sample size was relatively small. Data from male twins from the VET Registry suggested32 that shared environmental effects accounted for the comorbidity between conduct disorder and MJD. Empirical studies on genetic contributions to the comorbidity between MD and MJD are lacking.

Interpretation of the comorbidity and apparent shared genetic risk of MD and AD is complicated by the fact that conduct disorder21,35,69 and ASPD70-73 have also been found to be associated with increased risk of MD. The comorbidity between ASPD and MD could itself be due to common genetic risk factors, which may be an important confounding factor in studies60,64 of shared genetic risk between MD and AD. However, the genetic and environmental contributions to the interrelationships among ASPD, MD, AD, and MJD have not yet been explored, to our knowledge. Given that the onset of ASPD (or at least of conduct disorder) often precedes the development of substance dependence,74 it is natural to question whether the genetic correlations between MD and substance use disorders are secondary to the association between ASPD and those disorders.

We report the results of multivariate analyses of structured diagnostic interview data from twins from the VET Registry36 that directly test the hypothesis that shared genetic risk among ASPD, AD, and MJD is a major determinant of the shared genetic risk between MD and AD and between MD and MJD.

**METHODS**

**SAMPLE**

The VET Registry is a general population registry of male twins constructed in the middle 1980s from computerized Department of Defense files and other sources. Twins born between 1939 and 1957 who served on active military duty during the Vietnam era (1965-1975) were included. Zygosity was assessed using a series of questions about sibling similarity supplemented with limited blood group data obtained from military records. Zygosity determination using such methods has been shown to have 95% accuracy.75 The development and characteristics of the Registry have been published elsewhere.76,77 Registry members participating in research studies have been found to be representative of twins who served in the military during the Vietnam era on a variety of sociodemographic and other variables.77,78

The data reported here are from structured diagnostic telephone interviews administered to the VET panel in 1992.49 Of 10 300 eligible individuals, 79.7% completed the interview. The overall pairwise response rate was 66.0% (3372 complete pairs). A total of 3360 pairs (1868 MZ and 1492 dizygotic [DZ]) in which both members completed the pertinent diagnostic interview sections are included in the present study. The mean±SD age at interview of respondents was 42.0±2.7 years (range, 33.0-52.0 years); 93.8% were non-Hispanic white, 5.8% were African American, less than 1% were Hispanic, and 0.3% were of other ethnicity; 33.3% were high school graduates and 38.7% were college graduates; and 92.6% were employed full-time, 1.8% were employed part-time, and 5.6% were unemployed. Further details of the sociodemographic characteristics of the VET panel can be found elsewhere.30,44,49

**ASSESSMENT OF PSYCHIATRIC DISORDERS**

A computerized telephone version of the Diagnostic Interview Schedule, Version 3, Revised,79 was used to assess drug use and abuse or dependence and other axis I psychiatric disorders in all respondents. Experienced interviewers from the Institute for Survey Research at Temple University were trained by one of the project investigators (M.J.L.) to administer the telephone interview. The interview was administered after the respondent had given verbal consent. Lifetime diagnoses of ASPD, MD, AD, and MJD were determined according to DSM-III-R criteria.80 All diagnostic variables were coded dichotomously. Earlier analyses44,49 of VET Registry data reported good test-retest reliability of diagnostic measures. Because of the high prevalence in this male veteran sample of DSM-III-R AD as assessed by the Diagnostic Interview Schedule, Version 3, Revised, some analyses were repeated using a diagnosis of severe AD according to the DSM-III-R, operationalized following the Diagnostic Interview Schedule, Version 3, Revised, as the reporting of at least 7 symptoms with evidence of interference in occupational functioning or usual social activities or relationships with others.

**STATISTICAL ANALYSES**

Univariate and multivariate logistic regression analyses were performed to analyze the associations of AD and MJD with ASPD and with MD using statistical software (Stata, release 6.0; Stata Corp, College Station, Tex). Odds ratios and 95% confidence intervals (CIs) were estimated using the Huber-White robust variance estimator (Stata) to correct for the correlation between 2 members of each twin pair (which would otherwise lead to underestimation of 93% CIs for the odds ratios).

Genetic analyses of twin pair data used a normal liability threshold model85 to decompose the total phenotypic variance in risk of each disorder (“liability”) into genetic, shared environmental, and nonshared environmental components. Use of a threshold model implies the assumption, plausible for the specific disorders considered herein, that for each disorder there is a continuous and approximately normal distribution of risk in the general population, which is determined by the combined effects of multiple genetic and environmental risk factors. In univariate analyses, tetrachoric correlations (ie, correlations for liability to a disorder) are estimated separately for MZ and DZ pairs using standard maximum-likelihood methods.83,84 Under the assumption that MZ and DZ pairs do not differ in their concordance for pertinent shared environmental risk factors (eg, parental psychiatric disorders and neigh-
horhood risk factors), because MZ pairs are genetically identical and DZ pairs are genetically no more alike than ordinary full siblings, comparing MZ and DZ twin correlations provides a test for genetic effects. These twin pair tetrachoric correlations are used to estimate the contribution of genes and environmental (shared and nonshared) effects to variation in risk of a disorder. In this VET panel, there was little evidence for higher environmental correlations for MZ vs DZ twin pairs. The heritability of a disorder is defined as the proportion of the total variance in risk accounted for by genetic effects. In previous publications, univariate twin analyses of the VET sample showed significant additive genetic and nonshared environmental, but not shared environmental, effects on MD, ASPD, and AD and significant genetic and shared and nonshared environmental effects on MJD.

In the present study, our primary interest was in the interrelationships among the 4 disorders, so we extended the univariate analysis approach to the multivariate case. In multivariate analyses, 3 kinds of tetrachoric correlations (cross-twin within-variable, within-twin cross-variable, and cross-twin cross-variable correlations) were used to estimate the relative contributions of genetic, shared environmental, and nonshared environmental effects to the comorbidity of the 4 disorders. Results are summarized by genetic, shared environmental, and nonshared environmental correlations: for example, a genetic correlation of unity implies complete overlap of genetic risk factors for 2 disorders, whereas a genetic correlation of zero will occur if there is complete independence of genetic risk factors for the disorders. Similar interpretations may be given to the environmental sources of variation.

Matrices of tetrachoric correlations between the 4 disorders assessed in each twin (ie, 8 × 8 matrices) were estimated separately for MZ and DZ pairs using PRELIS 2. Multivariate genetic models were fitted by asymptotic weighted least squares using a structural equation modeling program (Mx; Virginia Commonwealth University, Richmond). We began by fitting a full Cholesky (“triangular decomposition”) model (Figure 1). For each source of variation (ie, genetic effects, shared environmental effects, and nonshared environmental effects), this model estimates as many latent factors as there are observed variables (ie, diagnoses), but with a triangular pattern of factor loadings. Thus, all observed variables are allowed to have nonzero loadings on the first factor; the second observed variable and all subsequent observed variables are allowed to have nonzero loadings on the second factor; the third and fourth observed variables (in our application) are allowed to have nonzero loadings on the third factor; and, finally, only the fourth observed variable is affected by the fourth factor. From this full model, predicted genetic and environmental variances in risk of each disorder, and genetic and environmental correlations between disorders, may be derived.

Under the full model, the ordering of observed variables is arbitrary, but this is not the case for submodels, in which 1 or more genetic or environmental factor loadings are fixed to zero. To test the hypothesis that the genetic correlations between MD and both AD and MJD could be entirely explained by genetic effects associated with ASPD, we fitted a submodel (model 4 in Figure 2) that estimated the first genetic factor with nonzero loadings of ASPD, MD, AD, and MJD; the second genetic factor with a nonzero loading of MD only (ie, fixing to zero the genetic paths to AD and MJD, thereby implying zero partial correlations between ASPD and both AD and MJD once genetic effects on risk of MD were controlled for); and the third and fourth genetic factors with the nonzero loadings shown in Figure 1. We compared this model with a model that reordered the diagnostic variables as MD, ASPD, AD, and MJD, with the first genetic factor having nonzero loadings on all variables but the second genetic factor having a nonzero loading on ASPD only (ie, fixing to zero the genetic paths to AD and MJD, thereby implying zero partial correlations between ASPD and both AD and MJD once genetic effects on risk of MD were controlled for), with third and fourth genetic factors again having the same nonzero loadings shown in Figure 1. Finally, under model 3 (Figure 2), we estimated likelihood-based 95% CIs for the proportion of the total genetic correlations between MD and AD and between MD and MJD that could be accounted for by the ASPD genetic factor.

The overall fit of each model tested was assessed using goodness-of-fit χ² (with P < .05 indicating a poor fit to the data) and the Akaike Information Criterion, with the lowest Akaike Information Criterion value indicating the most parsimonious model. The fit of nested models, in which the second model is a submodel of the first, with 1 or more factor loadings fixed to zero, was compared using the likelihood ratio test, with a statistically significant χ² value (P < .05) indicating that the second model gave a statistically significantly worse fit than the first.

RESULTS

Lifetime prevalence of DSM-III-R ASPD, MD, AD, and MJD in the VET Registry sample was 2.7%, 9.2%, 35.2%, and 6.6%, respectively. Lifetime prevalence of DSM-III-R se-

![Figure 1. Path diagram of the genetic and environmental interrelationships among antisocial personality disorder (ASPD), major depression (MD), alcohol dependence (AD), and marijuana dependence (MJD) for an individual twin under a Cholesky triangular decomposition model. The variance in liability for each disorder is partitioned into additive genetic (A), shared environmental (C), and nonshared environmental (E) effects. One-way arrows represent factor loadings used to compute variances. A, The additive genetic variance for ASPD is further partitioned into that shared with ASPD, MD, AD, and MJD-specific effects; the additive genetic variance for MD is partitioned into that shared with ASPD, MD, and AD specific effects; the additive genetic variance for MJD is partitioned into that shared with ASPD and MD and specific effects. B, The shared environmental variance for each disorder is similarly decomposed. C, The nonshared environmental variance for each disorder is similarly decomposed. All additive genetic, shared environmental, and nonshared environmental factor loadings were estimated simultaneously.](https://jamanetwork.com/)

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 associations among lifetime DSM-III-R diagnoses of ASPD, MD, AD, and MJD. A history of either ASPD or MD was associated with increased risk for lifetime AD, severe AD, or MJD compared with those without these disorders. Adjusted odds ratios for lifetime AD or MJD when both ASPD and MD were included as predictors were only modestly reduced compared with unadjusted odds ratios.

Model fit indices are summarized in Table 2. A companion path diagram (Figure 2) illustrates graphically the assumptions about genetic and shared environmental factors of the models compared. In multivariate twin analyses, 4 genetic, 4 shared environmental, and 4 nonshared environmental factors were estimated under the full model (model 1 in Figure 2). This model gave a good fit to the data ($P = .18$). Model 2, which tested the hypothesis of no genetic effect on any of the disorders by constraining to zero the paths from the 4 genetic factors to the 4 disorders, gave a very poor fit ($P < .001$). Model 3, which tested the hypothesis that there was no shared environmental effect on any disorder by fixing to zero all the shared environmental paths, gave a very good fit ($P = .39$). The fit of this model was not statistically significantly worse than that of the full model using the likelihood ratio test ($\chi^2_{10} = 5.3; P = .87$).

Under model 3, the paths from the genetic factor for MD ($A_{MD}$) to AD and to MJD were not statistically significant; therefore, we fixed them to zero to test the hypothesis that the genetic correlations between MD and both AD and MJD could be entirely accounted for by genetic effects associated with ASPD. This submodel (model 4) gave an excellent fit to the data ($P = .33$), and the fit of this model was not statistically significantly worse than that of model 3 ($\chi^2_{2} = 3.5; P = .17$). Model 4a tested the alternate hypothesis that the genetic correlations between ASPD and both AD and MJD could be entirely accounted for by genetic effects on MD, that is, the hypothesis that there were no significant residual genetic correlations between ASPD and both AD and MJD after controlling for genetic effect on MD. This submodel produced a poor fit to the data ($P = .02$) and a substantially worse fit than model 3 by AIC. These results were consistent with the hypothesis that genetic effects on ASPD are a major determinant of the genetic correlation between MD and both AD and MJD (models 3 and 4), but they did not support the alternate hypothesis that genetic effects on MD could account for the genetic correlation between ASPD and both AD and MJD.

Because previous studies from this twin panel suggested shared environmental effects on MJD, we also fitted a model that allowed for genetic and shared environmental effects specific to MJD (model 5). This model gave a fit as good as model 4, with neither genetic nor shared environmental effects specific to MJD being statistically significant, indicating that it was not possible to distinguish whether the remaining familial effects specific to MJD were genetic or shared environmental in origin. We therefore reported parameter estimates of genetic and shared environmental effects for the final model (model 5).

Under model 5 (see Figure 3 for genetic and environmental factor loadings), the heritabilities of lifetime DSM-III-R ASPD, MD, AD, and MJD were 69%, 40%, 11%, and 74%, respectively.

Figure 2. Path diagrams for the models compared in Table 2. Risk of antisocial personality disorder (ASPD), major depression (MD), alcohol dependence (AD), and marijuana dependence (MJD) (shown for an individual twin) is partitioned into additive genetic (A) and shared environmental (C) effects. In each model, factor loadings for nonshared environmental effects (E in Figure 1) (ie, no loadings were fixed to zero) are not shown. One-way arrows represent effects that were included in the model. Note that under model 4, there are no residual genetic correlations between MD and AD and between MD and MJD after controlling for the ASPD genetic factor (ie, the paths from $A_{ASPD}$ to AD and to MJD are omitted). Under model 4a, there are no residual genetic correlations between ASPD and AD and MJD after controlling for the MD genetic factor (ie, the paths from $A_{MD}$ to AD and to MJD are omitted).

vere AD was 6.9%. Thirty-six percent of respondents with ASPD met lifetime criteria for MD compared with 8% of those without a history of ASPD. Table 1 summarizes...
These analyses show that genetic effects associated with ASPD made a significant contribution to the genetic correlations between MD and AD and between MD and MJD. The residual genetic correlations between MD and AD and between MD and MJD were not statistically significant. Under model 3, we decomposed the total genetic correlations between MD and AD and between MD and MJD into 2 parts associated with MD and ASPD genetic factors, respectively. We found that 21.6% (95% CI, 0%-51.4%) of the total genetic correlation between MD and AD and 38.4% (95% CI, 0%-64.5%) between MD and MJD could be explained by the MD genetic factor and the remainder (78.4%; 95% CI, 49.6%-100%, and 61.6%; 95% CI, 35.5%-100%, respectively) by the ASPD genetic factor. This supports the original hypothesis that the genetic effects associated with ASPD largely account for the remaining genetic variance in risk of MJD after controlling for the MD genetic factor.

The contributions of nonshared environmental factors to the total phenotypic variance for MD, 28% for AD, and 29% for MJD. Furthermore, of the total genetic variances in risk for MD and AD, 38% (0.39^2/[0.502+0.39^2]) and 50% (0.53^2/[0.532+0.53^2]) were explained by the ASPD genetic factor. Approximately 58% (0.54^2/[0.542+0.082+0.45^2]) of the genetic and 46% (0.54^2/[0.542+0.082+0.452+0.36^2]) of the total familial (genetic and shared environmental) variance in risk of MJD was also accounted for by the ASPD genetic factor. After controlling for the ASPD genetic factor, the partial genetic correlations between MD and AD and between MD and MJD remained statistically significant. After controlling for ASPD and other genetic risk factors, the 95% CIs of genetic and shared environmental factor loadings specific to MJD were broad (95% CI, 0.0-0.65 and 0.0-0.58, respectively), suggesting that important genetic and shared environmental effects specific to MJD could not be excluded. We found statistically significant nonshared environmental effects on risk for each disorder. However, the contributions of nonshared environmental effects to the total phenotypic covariance among these 4 disorders were found to be small, indicating that nonshared environmental effects were less important in understanding the comorbidity among these 4 disorders.
for the genetic correlations between MD and AD and between MD and MJD.

**COMMENT**

In this US military veteran male twin sample, the interrelationships among DSM-III-R ASPD, MD, AD, and MJD almost entirely reflected common genetic (rather than common environmental) effects. Substantial proportions of the genetic variance in risk of AD and of the total familial (genetic and shared environmental) variance in risk of MJD were accounted for by genetic effects associated with ASPD. A history of ASPD predicted a 4-fold increase in the probability of reporting a history of MD, and 38% of the total genetic variance in risk of MD was associated with ASPD. Genetic effects associated with ASPD were a major determinant of the common genetic risk between MD and AD and between MD and MJD. Other researchers have reported a substantial genetic correlation between MD and AD. We believe that the present study represents the first attempt to parcel out effects attributable to ASPD from the overall genetic correlation between these 2 disorders. In these male twins, 78% of the genetic correlation between MD and AD and 62% of the genetic correlation between MD and MJD was explained by the genetic factor associated with ASPD, with these percentages not differing significantly from 100%.

Although the assessment of psychiatric disorders in the present study was based on lifetime diagnostic criteria, the model-fitting results suggest that, at least in men, the genetic correlations between MD and substance use disorders are largely secondary to the association between the genetic risk associated with ASPD and these disorders. This conclusion is supported by the fact that the alternative model (model 4a in Figure 2, reversing the order of ASPD and MD) did not fit the data well. In addition, the ordering of the psychiatric disorders in our model is supported by the temporal ordering reported by clinical and epidemiologic studies, although temporal ordering need not imply direction of causal effects.

Whether there are sex differences in determinants of the common genetic vulnerability between MD and AD needs to be addressed in future research in samples of female twins. It is possible that analyses of other data will determine that the contribution of ASPD to the genetic correlation between MD and AD is much less important in women than in men; such a sex difference could explain reports of a sex-specific genetic correlation between MD and AD. Consistent with this interpretation is the finding that ASPD and AD were genetically correlated in men but environmentally correlated in women and that genetic effects on MD in men and women were not perfectly correlated.

It is plausible that an important role of ASPD in accounting for shared genetic risk between MD and both AD and MJD will also be found for dependence on other classes of drugs. This possibility is suggested by family studies showing strong familial effects on the co-occurrence of different categories of drugs and by twin studies explicitly demonstrating genetic effect common to different classes of drug abuse or dependence.

The results of this study should be interpreted with several caveats. Our sample was composed of a relatively homogenous group of middle-aged and predominantly white male US military veterans, precluding generalization to women and other ethnic groups. Previous examinations of this twin panel (perhaps because of the ready availability of alcohol and drinking companions during military services) have observed a higher prevalence of AD and comparable figures for MD and MJD than was obtained from nonveteran men. The implications of these differences may limit the generalizability of our results to the general population, as discussed in detail in previous studies. It does not, however, seem that the broad AD phenotype identified by the Diagnostic Interview Schedule, Version 3, Revised, explains our results. When severe AD was predicted jointly from ASPD and MD, the association with ASPD was no less strong. Entry into military service probably excluded individuals with the most severe, early-onset antisocial behaviors. The much lower prevalence of DSM-III-R ASPD in this twin sample (2.7%) compared with that in men in the US general population (5.8%) supports this statement. This sample selection bias may have led to the disproportionate inclusion of individuals with ASPD who have mild to moderate antisocial behaviors but would be expected to attenuate rather than exaggerate associations between ASPD and AD. Heritability estimates of MD, AD, and MJD in this twin panel are similar to results from other nonveteran samples. Thus, it seems implausible that our findings are based on an artefactual contribution of ASPD to the genetic correlations of MD with AD and with MJD.

An additional limitation is that the models fitted are latent variable models, which do not attempt to specify causal relationships between variables at the phenotypic level. Thus, we cannot distinguish between the possibility that ASPD is itself a major mediator of genetic effects on risk of MD and risks for AD and MJD vs the possibility that there are genetic effects on impulsive traits that are associated with increased risk of ASPD, MD, and substance use disorders.

The results of the present study confirm that, at least in men, genetic effects on risk of ASPD are a major determinant of risk of substance dependence. Because of the strong comorbidity between ASPD and MD, failure to control for ASPD may have led to an overstatement of the importance of MD in the inheritance of AD and MJD.

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