

Genetic and environmental contributions to alcohol dependence risk in a national twin sample: consistency of findings in women and men

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ABSTRACT

Background. Genetic influences on alcoholism risk are well-documented in men, but uncertain in women. We tested for gender differences in genetic influences on, and risk-factors for, DSM-III-R alcohol dependence (AD).

Method. Diagnostic follow-up interviews were conducted in 1992–3 by telephone with twins from an Australian twin panel first surveyed in 1980–82 ($N = 5889$ respondents). Data were analysed using logistic regression models.

Results. Significantly higher twin pair concordances were observed in MZ compared to DZ same-sex twin pairs in women and men, even when data were weighted to adjust for over-representation of well-educated respondents, and for selective attrition. AD risk was increased in younger birth cohorts, in Catholic males or women reporting no religious affiliation, in those reporting a history of conduct disorder or major depression and in those with high Neuroticism, Social Non-conformity, Toughmindedness, Novelty-Seeking or (in women only) Extraversion scores; and decreased in 'Other Protestants', weekly church attenders, and university-educated males. Controlling for these variables, however, did not remove the significant association with having an alcoholic MZ co-twin, implying that much of the genetic influence on AD risk remained unexplained. No significant gender difference in the genetic variance in AD was found (64% heritability, 95% confidence interval 32–73%).

Conclusions. Genetic risk-factors play as important a role in determining AD risk in women as in men. With the exception of certain sociocultural variables such as religious affiliation, the same personality, sociodemographic and axis I correlates of alcoholism risk are observed in women and men.

INTRODUCTION

There is strong evidence from twin and adoption studies for an important genetic contribution to alcoholism risk in men (McGue, 1994; Heath *et al.* 1997a). This evidence is especially convincing in the case of studies using samples systematically

ascertained from birth or adoption records: adoption studies in Denmark (Goodwin *et al.* 1973, 1974), Sweden (Bohman *et al.* 1981; Cloninger *et al.* 1981, 1985; Sigvardsson *et al.* 1996) and Iowa, USA (Cadoret *et al.* 1985, 1987; Cadoret, 1994); and national twin studies in Sweden (Kaij, 1960; Allgulander *et al.* 1991, 1992; Kendler *et al.* 1997), Finland (Koshenvuo *et al.* 1984; Romanov *et al.* 1991) and the USA (Hrubec & Omenn, 1981; Reed *et al.* 1996; True *et al.* 1996), all suggest an important genetic

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contribution to male alcoholism risk. These studies cover birth cohorts ranging from the last century to the 1960s and early 1970s, and have used a variety of assessments of alcoholism including in-patient hospitalization or discharge codes, Veterans Administration treatment records, direct diagnostic interviews, registrations with the Swedish temperance boards for drunken behaviour or other evidence of alcohol problems and adoption record annotations about alcohol problems or excessive drinking in biological family members. Despite this methodological and sociocultural diversity, each of the six major twin studies has found a higher rate of alcoholism among monozygotic compared with dizygotic co-twins of alcoholic twins, although in individual studies this increase has often been non-significant (Heath *et al.* 1997a). Of the adoption studies, only a single study, the Catholic Adoption Agency study of Cadoret (1994) failed to find a higher rate of alcoholism among the adopted-away biological offspring of alcoholics, compared to control adoptees and even this negative finding may be explained by the abnormally high rates of alcohol abuse/dependence in the control adoptees in that study (58 % lifetime prevalence).

In contrast, evidence for a major genetic contribution to alcoholism risk in women from systematically ascertained adoptee and twin samples appears much weaker (McGue, 1994; Heath *et al.* 1997a). Significantly elevated rates of alcoholism in the adopted-away daughters of alcoholics have been reported in only two samples (Cadoret *et al.* 1985; Cloninger *et al.* 1985), with three studies producing negative results (Goodwin *et al.* 1977; Cutrona *et al.* 1994; Sigvardsson *et al.* 1996). Only three twin studies using samples ascertained from birth records have obtained data on alcoholism in female twin pairs. In a Finnish study using hospital discharge codes, no twin pairs concordant for alcoholism were found (Koskenvuo *et al.* 1984), thus making inferences about the causes or extent of familial aggregation impossible. In a comparable Swedish study, there was a trend for higher MZ than DZ twin pair concordance, which was however non-significant (Allgulander *et al.* 1992, 1993; Heath *et al.* 1997a). Finally, in the Virginia twin study, a survey based on personal interviews with some 1100 twin pairs identified from birth records,

there was no significant evidence for a genetic influence on DSM-III-R alcohol dependence risk (although there was a trend for higher MZ than DZ concordance), but significant effects were found for a more broadly defined problem drinking measure, and for a more narrowly defined dependence measure that also required symptoms of physiological dependence (tolerance or withdrawal) (Kendler *et al.* 1992).

Results from studies of twins ascertained from patient series, and their co-twins, also provide stronger evidence for a genetic influence on alcoholism risk in men than in women. Three studies (two by interview, one by mailed questionnaire) found higher rates of alcoholism (variously defined) in MZ compared to same-sex DZ co-twins of male alcoholic probands (Caldwell & Gottesman, 1991; Pickens *et al.* 1991; McGue *et al.* 1992), whereas a fourth interview study found no difference (Gurling *et al.* 1984). In three out of these four studies, however, there was essentially no difference in rates of alcoholism between MZ and DZ same-sex co-twins of female alcoholic probands (Gurling *et al.* 1984; Caldwell & Gottesman, 1991; McGue *et al.* 1992), while in the fourth study, for DSM-III abuse/dependence, differences were not significant (Pickens *et al.* 1991).

The absence of strong evidence for a genetic influence on female alcoholism has sometimes been interpreted as supporting the existence of a subtype of alcoholism ('type I') that is the predominant form among women and that is only modestly heritable, contrasted with a more highly heritable male-limited subtype ('type II': Cloninger, 1987). It has also led to a greater focus of high-risk research on adult male rather than female offspring of alcoholics (e.g. Begleiter *et al.* 1984; Schuckit & Smith, 1996). Failure to find statistically significant evidence for a genetic influence in women cannot however be interpreted as evidence that there is not an important genetic influence (as indeed some researchers have explicitly noted (Goodwin *et al.* 1977)). Such an interpretation ignores the low statistical power of individual twin and adoption studies for detecting genetic influences in women, a consequence of the much lower prevalence of alcoholism in women than in men. Indeed, re-analysis of individual studies using systematically ascertained samples did not in any instance find that a significantly higher proportion of the

variation in alcoholism risk could be explained by genetic factors in men than in women (Heath *et al.* 1997*a*). While one of four studies of clinically ascertained twin samples did report significantly higher heritability of alcoholism in men (McGue *et al.* 1992), this conclusion was highly dependent upon the statistical assumptions used in that paper (Heath *et al.* 1997*a, b*), with alternative assumptions again leading to the conclusion of no gender difference in alcoholism heritability.

In the present study, we seek to address two major gaps in the existing literature on the inheritance of alcoholism risk. The most convincing evidence for gender differences in the genetic contribution to alcoholism risk will come from within-study comparisons using very large sample sizes. The inclusion of unlike-sex as well as same-sex relative pairs is essential to provide a test of whether the same or different genetic or environmental risk-factors are influencing alcoholism risk in women as well as men (Neale & Cardon, 1992). If genetic factors are major determinants of alcoholism in men, whereas shared environmental factors are of predominant importance in women (McGue *et al.* 1992), then we would expect to find very low concordance of unlike-sex twin or parent-offspring pairs. None of the published general population twin studies has obtained such data. Findings from adoption studies that have assessed daughters as well as sons of alcoholic biological parents (usually fathers) have been inconsistent. Without such data, theories about gender differences in the inheritance of alcoholism risk must remain speculative.

It is also important that we progress to questions about the mechanisms by which genetic influences on alcoholism risk in men and women arise (Heath, 1993; Heath *et al.* 1997*b*), such as through heritable differences in personality (Cloninger, 1987; Heath *et al.* 1994*a*) or differences in alcohol sensitivity (Schuckit & Smith, 1996). Despite the extensive literature documenting the co-morbidity of alcoholism with other psychiatric disorders (e.g. Regier *et al.* 1990; Kessler *et al.* 1996), whose onset most often predates the onset of alcoholism (Kessler *et al.* 1996), few genetic studies have directly addressed the co-inheritance of alcoholism and other disorders. The one major exception, among the studies of population-based samples, as-

sessed women only (Kendler *et al.* 1993, 1995) and did not assess one of the most potent predictors of alcohol dependence risk, history of antisocial personality disorder or childhood conduct disorder (Robins & Regier, 1991). Other genetic studies have provided only limited data about the extent to which the inheritance of other psychiatric disorders may account for ('mediate': Baron & Kenny, 1986) genetic influences on alcoholism risk.

We present here findings from a telephone interview survey which obtained diagnostic assessments of DSM-III-R alcohol dependence in a large Australian volunteer twin panel. The study was designed to address some of the critical shortcomings of the existing literature on the genetics of alcoholism, by inclusion of unlike-sex as well as male like-sex and female like-sex twin pairs, and by assessment of common psychiatric disorders which frequently co-occur with alcoholism. Although not systematically ascertained from birth records, twins from the Australian twin panel were drawn from a variety of educational and socioeconomic backgrounds, and have been found in previous research to be comparable to the general population of Australia in their drinking habits (Jardine & Martin, 1984). Of particular importance, approximately 65% of the panel were women, and this fact combined with the large sample size gives the study acceptable power for detecting major gender differences in the genetic contribution to, and mediators of, alcoholism risk.

METHOD

Sample

Subjects were twins from a volunteer adult twin register, formed in 1978–9 and maintained by the Australian National Health and Medical Research Council (NH&MRC), who participated in a telephone interview follow-up survey in 1992–3 ($N = 3848$ women, average age 44.8 years, range 27–90; and $N = 2041$ men, average age 42.7 years, range 28–89). In 1979–81, 206 young adult twin pairs from the twin register, born 1944–63, had participated in an alcohol challenge study (Martin *et al.* 1985*a, b*). In 1980–82, both members of 3808 twin pairs and additional 567 single twins born 1893–1964 (including 132 pairs and 16 single twins from the

alcohol challenge sample), responded to a mailed questionnaire survey ('1981 survey': Jardine *et al.* 1984; Kendler *et al.* 1986). An 8-year follow-up was conducted in 1988–90 ('1989' survey: Heath *et al.* 1994a; Heath & Martin, 1994) with those pairs in which both twins had participated in the 1981 survey, with either questionnaire or abbreviated telephone interview data being obtained from 4116 women (84.5% follow-up rate) and 2211 men (80.5% follow-up rate). Eligible for inclusion in the 1992–3 telephone interview survey were: (i) all living twins who had participated in the alcohol challenge study; and (ii) all living twins from pairs where at least one twin had responded to the 1989 survey.

From the alcohol challenge sample, interview data were obtained from 187 out of the original 213 women subjects (87.8% response rate) and 162 out of 199 men (81.4% response rate). An additional five subjects were deceased, seven subjects were overseas and could not be contacted and 28 subjects were not contacted because they either could not be located or had previously requested that they not be contacted for further research studies. Excluding these cases, the cooperation rate in the interview follow-up for the subsample of alcohol challenge participants was 95.4% in women, 90.1% in men. For the 1981 survey sample (excluding alcohol challenge participants), from those pairs where at least one twin had responded to the 1989 survey, interviews were completed with 3659 eligible women (88.3%) and 1879 eligible men (82.5%). Excluding those who were deceased, overseas, not locatable, or who had previously withdrawn from the twin register, response rates from this subsample were 92.3% in women, 91.0% in men. Interviews were conducted with an additional 60 women and 46 men who had responded to the 1981 mailed questionnaire but were 'accidental' subjects, in that they did not meet eligibility criteria for the study. Interview data from these subjects are not used in analyses presented here.

In total, interview data were obtained from both members of 2685 pairs and from one twin only from an additional 519 pairs (see Table 1 below for distribution by zygosity). The excess of female like-sex pairs and of monozygotic pairs in part reflects the estimated zygosity distribution for the twin panel target sample for

the 1981 survey (1706 MZF, 901 MZM, 1113 DZF, 630 DZM and 1617 DZ unlike-sex pairs: Heath *et al.* 1995) and is a well-established phenomenon for volunteer twin panels (Lykken *et al.* 1978). In addition, however, consistently higher response rates have been achieved for female than for male respondents and for monozygotic compared with dizygotic pairs. For the 1981 survey, for example, response rates were 74.5% for MZ female twins, 72.5% for DZ female like-sex twins, 66.3% for MZ male twins, 63.5% for DZ male like-sex twins, 61.2% for DZ unlike-sex pair female twins and 58.1% for DZ unlike-sex male twins.

All participants in the telephone interview survey gave oral consent to participate in the research, after the elements of informed consent had been reviewed with them verbally.

Assessments

Because the Australian twin panel is a national sample, all interviews were conducted by telephone. A structured diagnostic interview that had been designed for genetic studies on alcoholism, the SSAGA (Bucholz *et al.* 1994) was adapted for telephone use. In within-centre and between-centre reliability studies reported for the full instrument, excellent reliability estimates were found for DSM-III-R alcohol dependence (κ s = 0.84, 0.89 respectively: Bucholz *et al.* 1994). Diagnostic assessments in the adapted SSAGA (SSAGA-OZ) included lifetime history of DSM-III-R alcohol dependence as well as other major psychiatric disorders and family history assessment of parents and co-twin. Interviews were conducted by a team of 20 lay-interviewers, who received 2 weeks of basic training in structured interviewing plus continuing in-service training. For quality-control, all interviews were audiotaped, unless the interviewee refused permission. Separate interviewers interviewed each member of a twin pair, so that interviews were conducted without prior knowledge of the history of the twin or his or her co-twin or family members.

A DSM-III-R alcohol dependence diagnosis was assigned by computer algorithm (American Psychiatric Association, 1987). Adaptation of the SSAGA for telephone administration did not appear to adversely affect its reliability. An independent repeat assessment of life-time his-

tory of alcohol dependence was obtained from 1117 female twins, during the period 1994–6; test–retest reliability (tetrachoric correlation \pm standard error) was 0.77 ± 0.04 . For family history data, a positive parental history of alcohol-related problems was inferred if either or both twins reported that a parent had alcohol-related problems with health, family, job or police, or similar problems (Slutske *et al.* 1996). A positive co-twin history of alcohol problems was inferred if at least two alcohol-related problems were identified by the respondent. Agreement between self-report history of alcohol dependence, and co-twin's family history report that the respondent had two or more alcohol problems was also good (tetrachoric correlations: female twins $N = 3492$, $r = 0.69 \pm 0.035$; male twins $N = 1812$, $r = 0.65 \pm 0.030$). However, for genetic analyses, we used only self-report measures of alcohol dependence.

DSM-III-R conduct disorder, major depression, social phobia, agoraphobia and panic diagnoses were also assigned by computer algorithm. The algorithm for conduct disorder did not use information about clustering of symptoms and considered conduct problems occurring before age 18. The assessment of major depression included sufficient information about impairment and clinical significance to permit diagnosis according to updated DMS-IV criteria.

Sociodemographic variables were taken from the baseline questionnaires obtained in the 1981 survey and the alcohol challenge study, with the former used wherever possible. Educational level was collapsed to a four-point scale: (i) early school leavers with no further educational training or apprenticeship; (ii) at least some high school, a diploma, trade certificate or apprenticeship; (iii) technical or teacher's college; or (iv) university education or higher. Wherever possible, education data were updated using information from a mailed questionnaire survey conducted in 1988–9 ('1989 survey'), based on information provided by either the respondent or, if unavailable, the respondent's co-twin, since many of the 1981 survey participants had not completed their education at the time of the baseline survey. Religious affiliation was collapsed to a five-point scale. Because church attendance (weekly *versus* less often) was not

assessed in the alcohol challenge study questionnaire, data were imputed for those participants who did not complete the 1981 survey using a logistic regression equation incorporating data on birth cohort, religion, marital status and educational background.

Both the 1981 survey and the alcohol challenge study had included as a personality assessment the Eysenck Personality Questionnaire (Eysenck & Eysenck, 1976; Eaves *et al.* 1989). This included the following scales: Extraversion (E), predominantly a measure of sociability and liveliness; Neuroticism (N), which assessed both anxious and depressive traits; Social Non-conformity (termed the 'Lie Scale' by Eysenck: L), which seems to assess prosocial versus mild anti-social traits; and Toughmindedness (termed 'Psychoticism' by Eysenck: P), a scale that is factorially and etiologically complex (Heath & Martin, 1990) and includes measures of suspiciousness, non-conformity and hostility towards others. Additional personality data, based on a shortened version of Cloninger's Tridimensional Personality Questionnaire (Cloninger *et al.* 1991; Heath *et al.* 1994a) were obtained from those respondents who returned a mailed questionnaire in the 1989 survey. This included assessments of personality traits Harm Avoidance, Novelty Seeking and Reward Dependence that had been hypothesized to be important mediators of genetic influences on alcoholism risk (Cloninger, 1987).

Data-analysis

Descriptive analyses

Estimates of the lifetime prevalence of alcohol dependence were computed for the entire sample of males and females, and by birth cohort, using both unweighted data and data weighted to adjust for non-random attrition, and for over-representation of well-educated respondents in the Australian twin panel (Baker *et al.* 1996). Sample weights used were a product of attrition weights estimated by logistic regression analysis to correct for non-random attrition between baseline and follow-up (Heath *et al.* 1997c) and education weights estimated from Australian Bureau of Statistics data on educational attainment (ABS, 1993) to correct the attrition-adjusted data for an initial cooperation bias with respect to educational attainment (Heath *et*

al. 1997d). Technical details of the use of data-weighting with data on twin pairs are given elsewhere (Heath *et al.* 1997c, d). Bootstrapped standard errors were estimated (Efron & Tibshirani, 1986), by resampling with replacement twin pairs with at least one twin participating in the follow-up interview, to adjust both for the reduced effective sample size associated with using sample weights, and for the non-independence of observations on twin pairs. Three thousand bootstraps were run for each analysis. Estimates of twin-pair probandwise concordance rates (i.e. the probability that the co-twin of an alcoholic twin would also have a history of alcoholism, estimated as $2C/(2C+X)$, where C is the number of concordant alcoholic pairs, and X the number of discordant pairs), and their standard errors, were similarly derived, using both unweighted data and data weighted using twin pair weights (Heath *et al.* 1997c, d). In this way we were able to examine the effects of over-representation of university-educated respondents and selective attrition, on our conclusions about the familial aggregation of alcoholism risk and its genetic or environmental origins. To test for possible effects of greater similarity of experiences of MZ compared to DZ same-sex pairs, proband-wise concordances were also computed separately for pairs reporting dissimilar *versus* similar early childhood experiences, or infrequent *versus* frequent social contact at the time of the baseline survey.

Descriptive analyses of the association between lifetime history of DSM-III-R alcohol dependence and both sociodemographic measures and co-twin's alcoholism history were conducted using multiple logistic regression analysis, with 95% confidence intervals for odds ratios again estimated by bootstrapping. We tested the statistical significance of the association between alcohol dependence and co-twin's history of alcohol dependence, controlling for age-cohort and sociodemographic variables. For each gender, five dummy variables were created to code co-twin's zygosity and alcoholism status. In these analyses, parental alcoholism history was not included as a predictor variable, since there is no straightforward interpretation of odds ratios for parental alcoholism when co-twin's alcoholism is already included as a predictor variable. Analyses were then extended

by the inclusion of measures of respondents' baseline personality traits and lifetime history of other DSM-III-R axis I disorders as predictor variables in the stepwise regression analysis, with sociodemographic variables identified as significant predictors in the prior step forced into the regression equation.

To test for residual genetic and/or shared environmental influences on alcoholism risk that were not mediated by effects on personality, sociodemographic variables or co-morbid psychiatric disorders, we examined the significance of the residual association between the respondent's and co-twin's alcoholism when these former variables were controlled for. Failure to find a significant residual association would be open to several possible interpretations. However, demonstration of a significant partial odds ratio for the relationship between alcoholism and co-twin's alcoholism history when these sociodemographic, personality and axis I variables were controlled for would be an important indicator of the incompleteness of our implied model for the inheritance of alcoholism risk.

Genetic model-fitting

As a final step, standard genetic model-fitting procedures (Eaves *et al.* 1978; Kendler *et al.* 1986; Neale, 1994) were used to obtain estimates of the proportion of the total variance in alcoholism risk that could be explained by additive genetic factors, environmental influences shared by members of a twin pair (e.g. home environment, rearing history) and non-shared environment (i.e. environmental influences not shared by twin pairs). Estimates were obtained under a multifactorial threshold model, which assumes that a continuous normal liability distribution underlies the observed binary distribution of absence *versus* presence of a history of alcoholism, and that the distribution of twin pairs for this latent liability variable is bivariate normal. These are the standard assumptions used in the estimation of tetrachoric and polychoric correlations (Tallis, 1962; Joreskog & Sorbom, 1993) and appear reasonable for a multifactorial disorder such as alcoholism (Heath *et al.* 1997b).

Models were fitted to the observed summary statistics for each zygosity group, i.e. the numbers of concordant alcoholic, discordant,

and concordant unaffected twin pairs, and of alcoholic and unaffected singleton twins,¹ by the method of maximum-likelihood (Neale, 1994), yielding estimates of genetic and environmental variances, and an overall chi-square test of goodness-of-fit. The fit of the most general model, estimating sex-dependent genetic and environmental parameters, with separate prevalence estimates for each zygosity group and for twins from complete pairs *versus* single twins, was compared by likelihood ratio (chi-square difference) test with submodels that assumed: (i) equality of alcoholism prevalences between complete pairs and singleton twins, and between individuals of the same gender from different zygosity groups; (ii) no genetic influence on alcoholism risk; (iii) no shared environmental influence on alcoholism risk; and (iv) no gender difference in the magnitude of genetic and environmental influences on alcoholism risk. Analyses were also conducted separately by birth cohort, and jointly pooling genetic and environmental parameters across birth cohorts, to provide a test for genotype \times cohort interaction, i.e. changes in the relative magnitude of genetic and environmental influences on alcoholism risk across birth cohorts (Heath *et al.* 1989a; Kendler *et al.* 1997); and for similar early experience *versus* dissimilar early experience pairs, to test for genotype \times environment interaction effects (Heath *et al.* 1989b). Likelihood-based 95% confidence intervals were computed for estimates of genetic and environmental parameters (Neale, 1994; Heath *et al.* 1997a). Confidence intervals were obtained by finding those fixed values of genetic or non-shared environmental parameters which led to a decrease in chi-square of 3.84 units when the remaining parameters were re-estimated. Point estimates of genetic and environmental parameters were also obtained using weighted data,

¹ Although often ignored in genetic studies, since they do not provide information about twin pair resemblance, inclusion of such singleton twins improves the precision of estimates of alcoholism prevalence, and thereby increases the precision of estimates of genetic and environmental parameters. Their inclusion also provides an important test for systematic undersampling of alcoholic twins that might bias estimates of genetic and environmental parameters: higher rates of alcoholism in the single twins compared with twins from complete pairs, or more frequent family history reports of co-twin's alcoholism by the single twins, would be indicative of such a problem.

to test for effects of sample attrition and over-representation of educated respondents on estimates of the heritability of alcohol dependence.

RESULTS

Prevalence of alcohol dependence

Fig. 1 summarizes estimates of the lifetime prevalence of DSM-III-R alcohol dependence (AD), by birth cohort, separately for women and men. Both unweighted estimates, and estimates using sample weights to adjust for the joint effects of selective attrition (with respect to twin pair zygosity, birth cohort, educational level, marital status and religious affiliation) and over-representation of university-educated respondents, are shown. In women, weighted estimates differed only slightly from unweighted

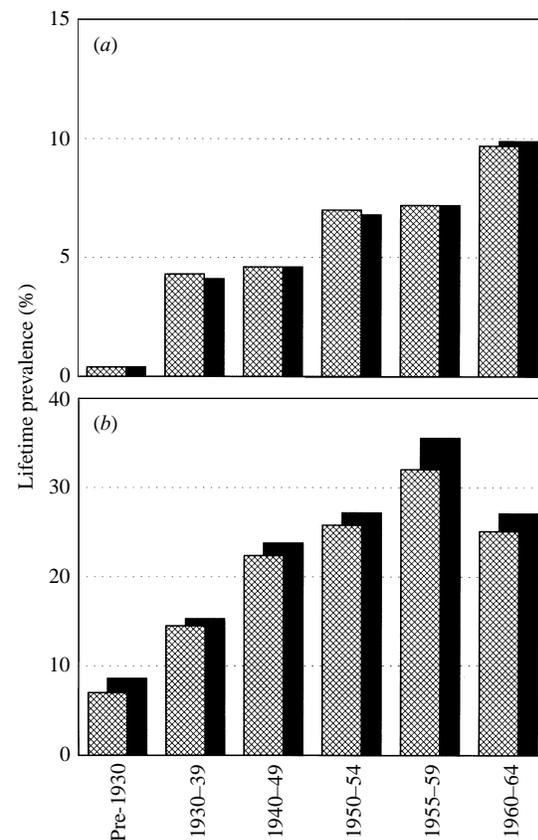


FIG. 1. Lifetime prevalence estimates (▨, unweighted; ■, weighted) by birth cohort for (a) women and (b) men.

Table 1. Lifetime prevalence, twin pair probandwise concordance rates and tetrachoric correlations for DSM-III-R alcohol dependence

Twin group	Sample size		Prevalence ^a				Probandwise concordance				Tetrachoric correlations	
	Complete pairs N Pairs	Single twins N Twins	Unweighted		Weighted ^b		Unweighted		Weighted ^b		ρ	S.E.
			%	S.E. ^c	%	S.E. ^c	%	S.E. ^c	%	S.E. ^b		
MZ female (MZF)	932	110	5.3	0.6	5.1	0.6	29.5	6.1	33.2	6.7	0.58	0.08
DZ same-sex female (DZF)	534	100	6.4	0.7	6.3	0.8	16.7	6.1	18.3	6.4	0.29	0.14
MZ male (MZM)	396	75	21.2	1.7	22.1	1.8	56.1	4.6	58.7	5.0	0.68	0.06
DZ same-sex male (DZM)	231	72	24.2	2.0	26.4	2.2	33.3	5.7	31.5	6.6	0.20	0.12
DZ unlike-sex (DZUS)	592	M: 48 F: 114	26.1	1.7	27.3	1.9	59.5 ^e	8.1	57.3 ^e	9.0	0.43	0.09
			6.4	0.9	6.2	0.9	14.0 ^d	2.8	11.3 ^d	2.6		

^a Prevalence estimates combine data from single twins and complete pairs, since there were no significant prevalence differences between these groups (MZF: $\chi^2_1 = 1.70$; DZF: $\chi^2_1 = 2.56$; MZM: $\chi^2_1 = 0.75$; DZM: $\chi^2_1 = 0.51$; DZUS: $\chi^2_2 = 0.88$; $P > 0.05$ in all cases). Overall unweighted prevalence estimates were 5.9% (S.E. 0.4%) for women, 25.2% (S.E. 1.3%) for men from DZ pairs and 21.1% (S.E. 1.6%) for men from MZ pairs. Corresponding weighted estimates were 5.6% for women, 21.9% for men from MZ pairs and 27.0% for men from DZ pairs. There were no significant differences in prevalence between zygosity groups in women ($\chi^2_2 = 1.59$, $P > 0.05$). However, prevalence was significantly lower in MZ male twins than in DZ male twins ($\chi^2_1 = 3.93$, $P < 0.05$), but did not differ between male DZ twins from same-sex versus unlike-sex pairs ($\chi^2_1 = 0.46$, $P > 0.05$).

^b Weighted analyses here and in the following tables used joint weights to adjust for over-representation of university-educated respondents and selective attrition.

^c Standard errors for estimates of prevalence and probandwise concordance rate were estimated by bootstrapping, to correct for data-weighting and non-independence of observations on twin pairs.

^d Risk to female co-twin of male alcoholic.

^e Risk to male co-twin of female alcoholic.

estimates, implying that the effects of these sampling biases were only modest. Reports of a history of AD in women born before 1930 were extremely rare (0.4% prevalence), with rates increasing in those born from 1930–49 (approximately 4.5%), still higher in those born 1950–59 (approximately 7%) and highest in the youngest cohort (9.7%). For the entire sample, the unweighted estimate for the lifetime prevalence of AD in women was 5.8%, almost identical to the estimates obtained using sample weights (5.7%).

In men, the unweighted prevalence estimates were consistently lower than the weighted estimates. The under-estimation of the lifetime prevalence of alcoholism was substantial in the oldest cohort of respondents born before 1930 (22.9% relative increase in estimated prevalence using weighted data), but otherwise was modest (5.5–10.9%). Alcoholism rates were high with a peak lifetime prevalence of 32.0% (weighted estimate 35.5%) in the 1955–9 cohort. Both unweighted and weighted estimates of the prevalence of AD had dropped in the youngest male cohort compared to the next-to-youngest, suggesting that this was a genuine phenomenon rather than an effect of greater attrition in the youngest cohort. For the entire sample, the

unweighted estimate of the lifetime prevalence of AD in men was 23.5%, compared to a weighted estimate of 24.9%.

Twin pair concordances

Table 1 summarizes for each zygosity group lifetime prevalence and probandwise concordance rate for DSM-III-R AD, and their standard errors, based on both unweighted and weighted data. Despite a significantly higher prevalence of AD in DZ male compared with MZ male twins and a non-significant trend in the same direction for female twins, the probandwise concordance rate was significantly elevated in MZ compared to same-sex DZ pairs, both in men (56% v. 33%) and in women (30% v. 17%), consistent with what would be predicted if there were a significant genetic influence on alcoholism risk in both genders. Weighting the data further strengthened the evidence for a genetic influence on AD, since it led to an increased prevalence estimate and reduced probandwise concordance estimate for male twins from DZ pairs and, to a lesser degree, from unlike-sex pairs.

Probandwise concordance rates were substantially higher for male than for female twins, as was to be expected given the pronounced gender difference in prevalence (a 4.3:1 ratio for

Table 2. Baseline sociodemographic and family history correlates of lifetime history of DSM-III-R alcohol dependence

	Women			Men	
	Odds ratio	95% CI*		Odds ratio	95% CI*
Born 1960–64	1.52	1.12–2.07	Born pre-1930	0.32	0.17–0.62
Other Protestant	0.64	0.44–0.92	Born 1955–9	1.40	1.09–1.79
No religion	1.98	1.34–2.92	University education	0.59	0.46–0.77
Weekly church attendance	0.44	0.27–0.69	Catholic	1.69	1.29–2.21
MZ co-twin alcoholic	4.17	2.17–8.01	Weekly church attendance	0.49	0.36–0.68
DZ female co-twin alcoholic	2.38 ^{NS}	0.78–7.31	MZ co-twin alcoholic	3.76	2.41–5.85
DZ male co-twin alcoholic	1.96	1.14–3.38	DZ female co-twin alcoholic	4.70	2.29–9.61
MZ co-twin unaffected	0.63	0.43–0.91	DZ male co-twin alcoholic	1.45 ^{NS}	0.81–2.58
DZ female co-twin unaffected	1.00	—	MZ co-twin unaffected	0.45	0.32–0.62
DZ male co-twin unaffected	0.51	0.28–0.93	DZ female co-twin unaffected	1.00	—
			DZ male co-twin unaffected	0.90 ^{NS}	0.63–1.28

* 95% confidence interval was estimated by bootstrapping, to adjust for non-independence of observation on twin pairs.

^{NS} Odds ratio not significantly different from unity.

male DZ compared with female twins). The concordance rate for male twins with female alcoholic co-twins (59.5%) was substantially greater ($P < 0.001$) than that for DZ male twins from same-sex pairs (33.3%). This is consistent with the hypothesis that, for the same level of genetic risk, women are much less likely to develop alcohol problems than men, so that on average women who become alcohol dependent have a higher genetic risk than men who become alcohol dependent.

Also given in Table 1 are unweighted estimates of twin pair tetrachoric (liability) correlations and their standard errors; weighted estimates were very similar. The observed 2:1 ratio of the twin pair correlations for MZ *versus* same-sex DZ pairs in women, and greater than 2:1 ratio in men, were consistent with the hypothesis that twin pair concordance for DSM-III-R AD is largely determined by shared genetic, rather than by shared environmental, risk. As can be seen from Table 1, there were no significant gender differences in either MZ or same-sex DZ correlations. Furthermore, the DZ unlike-sex pair correlation was somewhat higher than the two DZ same-sex correlations, in contrast to the reduced correlation that would have been predicted if there were important sex-specific genetic or shared environmental influences on alcoholism risk.

As noted in Table 1, there were no significant differences in prevalence between twins from complete pairs *versus* singletons, contrary to what would be expected if there had been

selective attrition of alcoholics from the baseline sample. There was also no significant association between non-participation in the interview and history of alcoholism as determined from the respondent's family history report about the co-twin, although there was a trend for higher rates of reported alcohol problems in male non-respondents. In the case of female non-participants, the proportion of respondents reporting two or more alcohol problems in their co-twins was 5.1%, as compared with 4.9% for female twins from pairs where both participated in the follow-up ($\chi^2 = 0.02$, $df = 1$, $P = 0.88$). In the case of male non-participants, corresponding proportions were 22.4% *v.* 19.1% ($\chi^2 = 1.67$, $df = 1$, $P = 0.20$). There was also no significant association between non-participation and parental history of alcoholism (women: $\chi^2 = 6.97$, $df = 3$, $P = 0.07$; men: $\chi^2 = 3.24$, $df = 3$, $P = 0.36$). Thus, it does not appear that there has been any major attrition with respect to alcoholism history.

As anticipated, we found greater concordance of MZ than DZ same-sex pairs for amount of social contact and for similarity of early environmental experiences. At baseline 53.9% of MZ male pairs and 55.8% of MZ female pairs reported seeing their co-twin at least weekly, compared to 44.4% and 45.7% of DZ same-sex male and female pairs, and 37.2% of unlike-sex pairs. MZ pairs were also more likely than same-sex DZ pairs to report that they usually or always shared the same peers when growing up (82.5% *v.* 52.3% in males, 82.7% *v.* 55.7% in

Table 3. Associations between DSM-III-R alcohol dependence and co-twin's alcoholism history, controlling for personality (EPQ, TPQ) and lifetime axis I disorders as well as sociodemographic variables

	Women				Men			
	Excluding TPQ (N = 3129)		Including TPQ (N = 2623)		Excluding TPQ (N = 1845)		Including TPQ (N = 1495)	
	OR	95% CI						
Childhood conduct disorder	4.63	2.65–8.08	4.92	2.57–9.43	1.89	1.40–2.55	1.82	1.28–2.59
Major depression	2.06	1.47–2.89	1.99	1.37–2.90	2.04	1.40–2.96	2.02	1.40–2.93
Social phobia	—	—	—	—	—	—	2.78	1.06–7.30
Extraversion > 75%ile	1.56	1.10–2.22	—	—	—	—	—	—
Social nonconformity 50–75%ile	1.92	1.27–2.91	1.80	1.13–2.86	1.46	1.09–1.95	1.00	—
Social nonconformity > 75%ile	2.23	1.49–3.33	2.16	1.37–3.39	1.68	1.22–2.32	1.47	1.03–2.11
Neuroticism 50–75%ile	1.00	—	—	—	1.50	1.11–2.03	1.48	1.04–2.09
Neuroticism > 75%ile	1.55	1.10–2.18	—	—	1.87	1.39–2.51	1.90	1.34–2.69
Toughmindedness > 75%ile	1.40 ^{NS}	1.00–1.98	1.52	1.03–2.23	1.63	1.24–2.14	1.60	1.17–2.20
Novelty seeking > 75%ile	—	—	1.63	1.09–2.43	—	—	1.66	1.19–2.31
MZ co-twin alcoholic	3.58	1.65–7.77	2.82	1.19–6.69	3.56	2.21–5.73	4.12	2.41–7.06
DZ female co-twin alcoholic	1.95 ^{NS}	0.62–6.06	0.76 ^{NS}	0.19–3.06	4.41	2.15–9.06	3.96	1.72–9.14
DZ male co-twin alcoholic	1.79 ^{NS}	0.98–3.25	1.49 ^{NS}	0.74–2.98	1.33 ^{NS}	0.72–2.46	1.47 ^{NS}	0.69–3.11
MZ co-twin unaffected	0.71 ^{NS}	0.48–1.04	0.71 ^{NS}	0.46–1.10	0.49	0.33–0.73	0.49	0.33–0.72
DZ female twin unaffected	1.00	—	1.00	—	1.00	—	1.00	—
DZ male co-twin unaffected	0.54 ^{NS}	0.29–1.03	0.41	0.18–0.94	0.90 ^{NS}	0.62–1.30	0.90 ^{NS}	0.59–1.38

Partial odds ratios were estimated from a multiple logistic regression analysis, using unweighted data.

females), and more likely to report usually or always being in the same classes at school (68.2% v. 46.5% in males, 78.4% v. 54.6% in females). However, when twin pair tetrachoric correlations for AD were recomputed separately for pairs with similar *versus* dissimilar environments, and with high *versus* low degrees of social contact, only a single significant difference was found out of a total of 20 comparisons, no more than would be expected by chance alone. Greater MZ than DZ twin pair correlations for these and associated environmental variables cannot explain the higher MZ than DZ concordances for alcoholism risk.

Sociodemographic correlates of alcohol dependence

Shown in Table 2 are the significant associations between sociodemographic variables and lifetime history of AD. Data from women exclude those born prior to 1930, since only two respondents from that cohort reported AD. In women, reporting a religious affiliation of 'Other Protestant', or at least weekly church attendance, was associated with decreased alcoholism risk, whereas reporting no religious affiliation was associated with increased risk. No significant associations with educational level, twin pair

zygosity type or marital status were found. Controlling for these sociodemographic variables, compared to alcoholism rates in women with an unaffected DZ twin sister, alcoholism risk was significantly reduced in those with an unaffected MZ twin sister (OR = 0.6, 95% CI = 0.4–0.9), and significantly elevated in those with an alcoholic MZ sister (OR = 4.2, 95% CI = 2.2–8.0), consistent with the hypothesis of a genetic influence on alcoholism risk. (The association between AD and having an alcoholic DZ sister – OR = 2.4, 95% CI = 0.8–7.3 – was not significantly less than with having an alcoholic MZ sister, but this reflects the very broad 95% confidence interval for the former odds ratio.) Analyses based on weighted data did not change these conclusions, except that the negative association with Other Protestant religious affiliation fell just short of significance.

In men, alcoholism rates were significantly elevated in those reporting a Catholic religious affiliation; and were significantly reduced in those with a university education, those born prior to 1930, and those reporting at least weekly church attendance. Controlling for these variables, alcoholism rates remained significantly higher in the co-twins of MZ compared to male same-sex DZ alcoholic twins (MZ:

OR = 3.8, 95% CI 2.4–5.9; DZ: OR = 1.45, 95% CI = 0.8–2.6), consistent with a significant genetic influence on alcoholism risk in men. The substantially elevated risk to male DZ co-twins of alcoholic sisters (noted in our results for twin pair concordance estimates) also persisted. These conclusions were unchanged when weighted data were used.

Personality, psychopathology and alcoholism risk

Table 3 shows the associations with AD of the respondents' own baseline personality scores and self-report history of psychopathology, controlling for sociodemographic variables (not shown) in a multiple logistic regression analysis in which co-twin's alcoholism history was also included. Separate analyses are reported: (i) using only baseline personality measures; and (ii), for a smaller subsample, including additional TPQ personality measures in the 1989 survey follow-up. In women, the strongest association with AD was found for history of childhood conduct disorder (OR = 4.6), but associations were also found with lifetime history of major depression (OR = 2.1), and with scores in the highest quartile on baseline measures of extraversion and neuroticism (OR = 1.6 in each case), and scores above the median on social non-conformity (OR > 1.9). Neither panic disorder nor social phobia were significantly associated with AD when other variables were controlled for. When data from the TPQ were included, only in the case of novelty seeking scores above the 75% percentile (OR = 1.6) was there a significant improvement in the statistical prediction of alcoholism risk. In both analyses, there remained a significant and substantial residual association between MZ co-twin's alcoholism and AD, after adjusting for the effects of sociodemographic and personality variables and axis I disorders. For the latter analysis the risk to the MZ co-twin of an alcoholic sister was significantly greater than to the DZ co-twin, but in the former analysis this difference was no longer significant, so that it was no longer possible to determine whether this residual association was due to shared genetic or shared environmental influences. Once again, weighted analyses did not change these conclusions (not shown).

Predictors of AD in men were in most respects

the same as those observed in women, except that the association with history of conduct disorder was weaker (OR = 1.9), there was no association with baseline extraversion score but a stronger association with baseline neuroticism, and there was also a marginal association with history of social phobia in the analysis including TPQ variables. After controlling for these variables, there remained a significantly elevated risk to the MZ co-twins of alcoholics compared to DZ co-twins (MZ: OR = 3.6, 95% CI 2.2–5.7; DZ: OR = 1.3, 95% CI = 0.7–2.5), and a significantly reduced risk in MZ co-twins of non-alcoholics compared to DZ co-twins (MZ: OR = 0.5, 95% CI 0.3–0.7, DZ: OR = 0.9, 95% CI = 0.6–1.3), consistent with what we would expect if there was a significant residual genetic influence on AD that was not associated with differences in personality, history of major depression and conduct disorder and socio-demographic variables. As in women, weighted analyses did not alter these conclusions (not shown).

Alcoholism heritability in men and women

Table 4 summarizes the results of fitting genetic and environmental models, including formal statistical tests for gender differences in the magnitude of genetic and environmental influences on alcoholism risk. These analyses confirm significant genetic influences in both genders (models 2 and 3 rejected), but give no evidence for either gender-specific genetic effects or gender differences in the proportion of the total variance in alcoholism liability accounted for by genetic differences (models 5, 6 give acceptable fits). They also show no significant shared environmental influences on alcoholism risk (model 4 gives an acceptable fit). Under a model allowing for genetic, shared and non-shared environmental influences, estimates of the proportions of the total variance in alcoholism liability attributable to each of these sources, and their 95% confidence limits, were respectively 64% (32–73%), 1% (0–27%) and 35% (27–47%). Analyses using weighted data produced very similar estimates: 66.1%, 0% and 33.9%. When the same analyses were conducted separately for each birth cohort (not shown), a similar picture emerged, with no significant gender difference in the genetic contribution to alcoholism risk for any of the

Table 4. Results of fitting genetic models and likelihood-ratio tests for key hypotheses

Genetic effects	Model		Goodness-of-fit		Hypothesis	Model-comparison		Likelihood-ratio test		Outcome
	Shared environment effects	Non-shared environment effects	df	χ^2		P	df	χ^2	df	
1. M ≠ F	M ≠ F ^b	M ≠ F	9	11.33	0.25	—	—	—	—	—
2. M ≠ F, M = 0	M ≠ F ^b	M ≠ F	10	24.07	< 0.01	2 v. 1	12.74	1	< 0.001	REJECT
3. M ≠ F, F = 0	M ≠ F ^b	M ≠ F	10	18.52	< 0.05	3 v. 1	7.19	1	< 0.01	REJECT
4. M ≠ F	NO	M ≠ F	12	11.36	0.50	4 v. 1	0.03	3	0.86	ACCEPT
5. M ≠ F ^c	NO	M ≠ F	11	11.36	0.41	5 v. 4	0.00	1	1.00	ACCEPT
6. M = F	NO	M = F	13	11.74	0.55	6 v. 4	0.38	1	0.54	ACCEPT

All analyses used unweighted data from both complete pairs and single twins, and included separate prevalence estimates for women, MZ men and DZ men.

^a Separate parameters were estimated for males and females.

^b Model also allowed for sex-specific shared environmental effects.

^c Model also allowed for sex-specific genetic effects.

cohorts where such an analysis was possible (i.e. all but the oldest cohort), and remarkable consistency of heritability estimates across cohorts (1960–64: 68%; 1955–9: 60%; 1950–54: 63%; 1940–49: 47%; pre-1940: 75%). These estimates were not significantly heterogeneous ($\chi^2 = 3.15$, $df = 4$, $P = 0.53$). Similarly, when we tested for genotype \times environment interaction effects by testing for heterogeneity of genetic effects on alcoholism in twin pairs reporting at least weekly *versus* less frequent social contact, and in twin pairs reporting always or usually *versus* only sometimes sharing the same peers when growing up, no significant differences in genetic or environmental influences on alcoholism risk was observed ($\chi^2 = 2.85$, $df = 2$, $P = 0.24$; $\chi^2 = 3.18$, $df = 2$, $P = 0.19$).

DISCUSSION

Genetics of alcohol dependence

Our results suggest that the heritability of AD – the proportion of the total variance in DSM-III-R alcohol dependence risk that is explained by genetic differences – is equally great in women and in men, with approximately two-thirds of the variance in risk of alcoholism being attributable to genetic factors. This estimate is imprecise (95% confidence limits are 32–73%), so that a substantial gender difference in heritability could remain undetected, but is quite consistent with estimates for men and women derived from findings from other general population twin and adoptee samples (Heath *et al.* 1997a). We also failed to find evidence for changes in the genetic contribution to alcoholism risk as a function of birth cohort, obtaining remarkably consistent estimates (range: 47–74%). This conclusion of equal alcoholism heritability in women and men does not imply equal lifetime risks to male and female relatives of alcoholic probands. As in other societies (e.g. Helzer *et al.* 1990), we find a large difference in alcoholism rates as a function of gender, with sex-ratios ranging from almost 5:1 in those born before 1940, to 2.6:1 in those from the youngest birth cohort born 1960–64. Our data rather support the conclusion that women with the same degree of genetic risk as men are less likely to become alcoholic. Thus, whereas one-third of the male dizygotic co-twins of males with a history of AD also had a history of AD, this was

true for only 14% of female dizygotic co-twins of male AD twins. An implication of this interpretation is that women who do develop alcohol-related problems will on average be at higher genetic risk than men who develop alcohol-related problems. Consistent with this, rates of alcoholism were substantially elevated in male co-twins of alcoholic female sisters, with some 60% positive for lifetime history of alcohol dependence.

Demonstrating comparably high heritability of alcohol dependence in women and men leaves unanswered the question of how genetic influences on alcoholism risk arise. A narrow 'medical genetic' model of alcoholism (Heath, 1993), which ignores the intervening behaviours through which problems with alcohol develop, would appear to be inappropriate. Results from the logistic regression analyses presented in Table 3 suggest that history of childhood conduct disorder – which in this sample appears to be strongly influenced by genetic factors (Slutske *et al.* 1997a) – may be one important mediator of genetic influences on alcoholism risk, especially in women. Indeed, history of conduct disorder in women differed from other variables in being more strongly associated with alcoholism risk than even MZ co-twin's alcoholism (odds ratios of 4.6 and 3.6 respectively). History of major depression was also modestly associated with alcoholism risk in both genders (odds ratios of 2.0). Since we are dealing with a general community sample in which most cases of AD will be mild (Heath *et al.* 1994b) – reflected in the high prevalence estimates – it is unlikely that this association is merely a secondary consequence of depressed affect occurring in the context of alcohol withdrawal (Schuckit, 1994). EPQ personality traits measured at baseline, which have been shown to be moderately heritable (Eaves *et al.* 1989; Heath *et al.* 1994a), were also associated with differences in alcoholism risk, most especially social non-conformity (L), which may be viewed as a measure of prosocial *versus* anti-social tendencies; but from the analyses presented here we cannot exclude the possibility that these personality differences are consequences of, rather than precursors of, differences in alcoholism risk. Disappointingly, the personality traits assessed by Cloninger's TPQ, though heritable (Heath *et al.* 1994a), do not appear in these data

to play a prominent role in the inheritance of alcoholism risk, with only novelty-seeking showing a modest association with lifetime history of alcoholism.

Environmental correlates

By conducting analyses within a logistic regression framework, we have tried to avoid understating the potentially important contribution of environmental variables (as well as sociodemographic variables such as educational attainment which may in part be genetically influenced: Vogler & Fulker, 1983; Baker *et al.* 1996) to differences in alcoholism risk. Roman Catholicism is an environmental variable for which MZ and DZ twin pairs exhibit very high concordance, but in males in this sample is associated with increased alcoholism risk. (It must be acknowledged, however, that in these data we cannot exclude the possibility that the association with Catholicism is secondary to an ethnic difference – Australians of Irish ancestry – which may in part reflect underlying genetic differences.) Regular church attendance in both genders, and reporting no religious affiliation in women, were also associated with differences in alcoholism risk, although for these latter variables we cannot exclude the possibility that drinking patterns led to a change in religious faith or practice.

Based on the results of genetic model-fitting analyses, we failed to find significant shared environmental influences on alcoholism risk, in either Australian women or men, with estimates of only 1% and 3% of the variance in alcoholism risk explained by shared environmental factors. This would imply that within this community sample such shared experiences as parental drinking and alcoholism, growing up in the same family and in the same neighbourhood, and attending the same school, are not important determinants of sibling resemblance for alcoholism, except in-so-far as these environmental differences interact with genetic differences. (Such genotype \times shared environment effects will be confounded with genetic effects in our data.) Even with sample sizes as large as in the present study, however, quite sizeable shared environmental effects could remain undetected: 95% confidence limits for the shared environmental contribution to variance in alcoholism risk were 0–30% for men and 0–43% for women.

Limitations

Several potential limitations of this study need to be considered. Our results, as indeed is the case with most other major twin and adoption studies on alcoholism risk, can only be generalized to individuals of European ancestry. The Australian twin panel is a volunteer panel, rather than a register of twins systematically ascertained from birth records, and somewhat over-represents well-educated individuals. Nonetheless, a broad range of educational and socioeconomic levels are represented in the sample, and we did not find these variables to be important predictors of alcoholism risk, suggesting that this non-representativeness with respect to education will not be an important source of bias. We cannot exclude the possibility that systematic sampling biases have occurred with respect to other, unmeasured variables that might be important determinants of alcoholism risk. However, the consistency of our findings using unweighted data *versus* data weighted to take into account the over-representation of well-educated respondents, and selective attrition with respect to baseline sociodemographic variables, gives greater confidence in the generalizability of our findings.

We have not attempted to identify more homogeneous subtypes of alcoholism, that might exhibit differences in mode of inheritance. Even in clinically ascertained samples, the identification of rules for subtyping that do not leave a high proportion of alcoholics unclassified has proved a daunting challenge. In this community sample, our attempts to identify subtypes having similar alcoholic symptom profiles, using latent class analysis, have identified groups differing in severity of alcohol problems, but have failed to find subtypes having distinctive alcoholic symptom profiles (Heath *et al.* 1994*b*). Similar results have been obtained using clinically ascertained samples assessed with the same diagnostic instrument (Bucholz *et al.* 1996).

The sample used in this study, like that of the Virginia twin study (Kendler *et al.* 1992), is a general population sample rather than a clinically ascertained sample. As a consequence, the majority of cases of alcoholism represented in the sample will be mild and typically untreated cases. This is apparent from the very high lifetime prevalence estimates reported for

Australian males (e.g. 32% for those born 1955–9). For the goal of incorporating a genetic perspective in prevention research on alcoholism, this is an important advantage, since the majority of individuals in the general population experiencing alcohol-related harm will be similarly mild cases (Heath *et al.* 1994*b*, 1997*b*). On the basis of these studies, however, we cannot make generalizations about what would be found in more severe alcoholics. Nonetheless, the very similar findings obtained in studies using samples ascertained from birth or adoption records, including studies which have identified more severe cases (e.g. identified from treatment or hospital records), and the consistency of findings of latent class analyses conducted using data from clinically ascertained *versus* high-risk samples, raise the possibility that we are dealing with a continuum of severity of alcohol-related problems, rather than with distinct aetiological processes for mild *versus* severe cases, as has sometimes been suggested (e.g. Goodwin *et al.* 1994).

Implications

The results of this study are consistent with an important genetic influence on risk of developing alcohol-related problems in both women and men. They also emphasize how little we understand about how such genetic influences arise. Personality variables, which have sometimes been proposed as major mediators of genetic influences on alcoholism risk (e.g. Cloninger, 1987), were found to be only weakly associated with differences in alcoholism risk. Even when personality and sociodemographic and axis I measures were controlled for, alcoholism in an MZ co-twin was associated with a significantly elevated risk of alcohol dependence (odds ratio 3.6 in both women and men), suggesting that much of the genetic variance in alcoholism risk is not mediated through these variables, but is acting through other pathways which remain to be determined. Differences in reactions to alcohol (Schuckit & Smith, 1996), leading to genetically determined differences in levels of consumption (Heath, 1995), may be one such pathway that deserves further exploration.

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