Psychological Medicine, 2004, **34**, 1519–1530. © 2004 Cambridge University Press
DOI: 10.1017/S0033291704002922 Printed in the United Kingdom

Genetic effects on alcohol dependence risk: re-evaluating the importance of psychiatric and other heritable risk factors

VALERIE S. KNOPIK*, ANDREW C. HEATH, PAMELA A. F. MADDEN, KATHLEEN K. BUCHOLZ, WENDY S. SLUTSKE, ELLIOT C. NELSON, DIXIE STATHAM, JOHN B. WHITFIELD AND NICHOLAS G. MARTIN

Missouri Alcoholism Research Center, Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA; Missouri Alcoholism Research Center, Department of Psychological Sciences, University of Missouri, Columbia, MO, USA; Department of Epidemiology and Population Health, Queensland Institute for Medical Research, Brisbane, Australia; Department of Clinical Biochemistry, Royal Prince Alfred Hospital, Sydney, Australia

ABSTRACT

Background. Genetic influences have been shown to play a major role in determining the risk of alcohol dependence (AD) in both women and men; however, little attention has been directed to identifying the major sources of genetic variation in AD risk.

Method. Diagnostic telephone interview data from young adult Australian twin pairs born between 1964 and 1971 were analyzed. Cox regression models were fitted to interview data from a total of 2708 complete twin pairs (690 MZ female, 485 MZ male, 500 DZ female, 384 DZ male, and 649 DZ female/male pairs). Structural equation models were fitted to determine the extent of residual genetic and environmental influences on AD risk while controlling for effects of sociodemographic and psychiatric predictors on risk.

Results. Risk of AD was increased in males, in Roman Catholics, in those reporting a history of major depression, social anxiety problems, and conduct disorder, or (in females only) a history of suicide attempt and childhood sexual abuse; but was decreased in those reporting Baptist, Methodist, or Orthodox religion, in those who reported weekly church attendance, and in university-educated males. After allowing for the effects of sociodemographic and psychiatric predictors, 47% (95% CI 28–55) of the residual variance in alcoholism risk was attributable to additive genetic effects, 0% (95% CI 0–14) to shared environmental factors, and 53% (95% CI 45–63) to non-shared environmental influences.

Conclusions. Controlling for other risk factors, substantial residual heritability of AD was observed, suggesting that psychiatric and other risk factors play a minor role in the inheritance of AD.

INTRODUCTION

The strong familial aggregation of alcoholism is well-established (Reich *et al.* 1988; Merikangas, 1990; McGue, 1994; Merikangas *et al.* 1998), with controlled studies of the families of alcoholic probands revealing a three-fold increased risk of alcoholism among the relatives of affected probands when compared to controls (Merikangas & Avenevoli, 2000). A family history of alcoholism has been shown to be the most consistent risk factor for developing alcohol dependence (AD), after personal alcohol use variables and pre-existing emotional

* Address for correspondence: Dr Valerie S. Knopik, Missouri Alcoholism Research Center, Department of Psychiatry, Washington University School of Medicine, 40 N. Kingshighway, Suite 1, St. Louis, MO 63108.
(Email: vsknopik@matlock.wustl.edu)

and behavioral disorders (Sher *et al.* 1991; Merikangas *et al.* 1998). Studies have also indicated that family history and individual history of psychopathology play a more significant role in the transition to problematic alcohol use and dependence than other individual characteristics and peer influences (Bucholz *et al.* 2000; Merikangas & Avenevoli, 2000); whereas the latter have been suggested to strongly affect exposure and initial patterns of alcohol and drug use (Pickens *et al.* 1991; Merikangas *et al.* 1998).

Twin and adoption studies indicate that genetic factors play a major role in the familial aggregation of AD. In the interview-based Danish adoption study, alcoholism in men was associated with alcoholism in biological but not adoptive parents (Goodwin *et al.* 1972, 1977). A similar association between record-based determination of alcoholism in adopted-away sons and their biological fathers was reported in Sweden (Cloninger *et al.* 1981; Sigvardsson *et al.* 1996). Likewise, the Iowa adoption studies (Cadoret *et al.* 1985*a*, 1987; Cadoret, 1994) showed a significantly elevated risk for AD in adopted-away sons and daughters from an alcoholic biological background, compared to control adoptees, consistent with a genetic influence on alcoholism. National and regional twin studies, both in the USA and abroad, of the risk of developing alcoholism in identical [monozygotic (MZ)] and fraternal [dizygotic (DZ)] co-twins of alcoholic twins have confirmed a higher risk to MZ compared to DZ co-twins of alcoholics, regardless of whether alcoholism was assessed by treatment or other official records (e.g. Hrubec & Omenn, 1981; Koskenvuo *et al.* 1984; Romanov *et al.* 1991; Kendler *et al.* 1997*b*) or by diagnostic interview (Kendler *et al.* 1992*a*; Heath *et al.* 1997*b*; Prescott *et al.* 1999; True *et al.* 1999). Across studies, genetic effects have been found to account for approximately 60% of the variance in alcoholism risk in both men and women of European ancestry (Heath, 1995; Heath *et al.* 1997*a*, *b*). These data also suggest no significant effect of family environment on the liability to develop AD.

Sociodemographic and family variables such as religious affiliation, religious involvement, educational level and childhood sexual abuse (CSA), and psychiatric risk factors such as childhood conduct disorder, antisocial personality disorder (ASPD), and major depression may play an important role in the familial transmission of AD, and (with the exception of purely cultural variables such as religious affiliation) in contributing to genetic influences on AD risk. Religiosity as measured by strong familial variables such as personal devotion and institutional conservatism, has been shown to be significantly and inversely associated with lifetime risk for AD (Kendler *et al.* 1997*a*). Similarly, Heath *et al.* (1997*b*) reported that weekly church attendance was associated with decreased alcoholism risk in both men and women. Educational level, which has been found to be associated with AD risk in some samples (e.g. Heath *et al.* 1997*b*), also shows strong familial transmission, which in recent birth cohorts, is largely genetically determined (Heath *et al.* 1985). CSA has also been shown, in general population studies, to increase risk for alcohol abuse and/or dependence (e.g. Fergusson *et al.* 1996; Spak *et al.* 1998; Kendler *et al.* 2000; Nelson *et al.* 2002) even after controlling for confounding effects of family background (Nelson *et al.* 2002). Important genetic influences have been reported for major depression (Cadoret *et al.* 1985*b*; Kendler *et al.* 1992*b*; Lyons *et al.* 1998; Bierut *et al.* 1999; Kendler & Prescott, 1999), childhood conduct disorder (Slutske *et al.* 1997; Jacobson *et al.* 2000) and adult ASPD or antisocial traits (Cloninger & Gottesman, 1987; Grove *et al.* 1990; Lyons *et al.* 1995). Both depression and ASPD have been shown to co-occur at higher than expected rates with AD (Kessler *et al.* 1997; Regier *et al.* 1990), and high genetic correlations have been reported between AD and history of childhood conduct disorder (Slutske *et al.* 1998) or ASPD (Fu *et al.* 2002), as well as significant genetic correlations between AD and history of major depression (Kendler *et al.* 1993; Prescott *et al.* 2000), although the role of ASPD as a confounding factor in the latter association cannot yet be discounted (Fu *et al.* 2002).

While it is clearly possible that psychiatric and sociodemographic risk factors may account for much of the familial variance in AD risk, existing studies have addressed this question in a limited fashion. One approach has been to fit multivariate genetic factor models to psychiatric outcomes including AD (e.g. Kendler

et al. 1995). However, finding a significant genetic correlation between risks of two disorders carries no necessary implication that one disorder is mediating some of the genetic influences on the second disorder. It could equally be the case that some intervening variables (e.g. genetically determined differences at the level of neurotransmitter systems) are contributing to risk of each disorder, with no direct effect of either disorder on the risk of the other. A second approach has been to use regression models, testing for zygosity differences in the association between respondent's and co-twin's AD history, after controlling for risk factors such as personality, religion, education, and psychiatric history (Heath *et al*. 1997*b*). However, with this method, no direct test of residual genetic influence on AD risk is conducted. Thus, the primary objectives of the present study focus on determining the role that sociodemographic and psychiatric variables play in mediating genetic influences on AD and are three-fold: (1) To identify risk factors for DSM-IV AD in both men and women; (2) to compare risk of AD in MZ and DZ twins as a function of co-twin history after controlling for the identified risk factors; and (3) to determine the extent of residual genetic and environmental influences on alcoholism liability, controlling for effects of sociodemographic and psychiatric predictors on risk.

METHOD

Participants and measures

The data for this analysis were collected from young adult twin pairs born between 1964 and 1971 who participated in a volunteer twin panel maintained by the Australian National Health and Medical Research Council. This sample is completely distinct from the older cohort of Australian twin pairs analyzed by Heath *et al*. (1997*b*). Twin pairs were ascertained as children in response to systematic appeals to parents through the Australian school systems and the mass media during the period 1980–1982; however, they were never assessed as children. Out of a total of 8020 twins (4010 pairs) ascertained as children, diagnostic interviews were conducted with 6207 twins (77·4% response rate), including both members of 2723 pairs. Non-participation was due to the following: partial interview (0·6%), deceased/incapable twins (2·1%), refusals (14%), unable to be contacted (5·1%), and no response (0·8%). After deleting observations with incomplete data, the present set of analyses includes data from a total of 2708 complete twin pairs (690 MZ female, 485 MZ male, 500 DZ female, 384 DZ male, and 649 DZ female/male twin pairs). All participants completed a telephone diagnostic interview conducted during 1996–2000. This interview was based upon a modified version of the SSAGA (Semi-Structured Assessment of the Genetics of Alcoholism; Bucholz *et al*. 1994; Hesselbrock *et al*. 1999), which was developed for the Collaborative Study of the Genetics of Alcoholism and is a comprehensive psychiatric interview used to assess physical, psychological, social, and psychiatric manifestations of alcohol abuse and dependence and related psychiatric disorders in adults (see Bucholz *et al*. 1994 and Hesselbrock *et al*. 1999 for reliability and validity data). Modifications were made to the SSAGA to incorporate DSM-IV (APA, 1994) criteria as well as to adapt it for telephone use. Verbal consent was obtained from all participants prior to their participation in the interview, using procedures approved by the Human Studies Committee at Washington University and the Ethics Committee at Queensland Institute of Medical Research.

The adapted SSAGA (SSAGA-OZ) included diagnostic assessments (DSM-IV) of AD, history of major depression, panic disorder, and childhood conduct disorder. Non-diagnostic measures of social anxiety and suicidality were also included. In addition to standard psychiatric assessment, information about CSA was collected. A binary composite CSA variable was constructed from five component questions regarding (*a*) forced sexual intercourse/activity before age 18, (*b*) sexual contact, before age 16, with someone other than a family member who was 5 or more years older than the respondent, (*c*) sexual contact, before age 16, with family members, (*d*) rape before age 18, (*e*) sexual molestation before age 18 (see Nelson *et al*. 2002 for more detail). A diagnosis of DSM-IV AD was assigned by computer algorithm. In addition, DSM-IV major depression, conduct disorder, and panic disorder diagnoses, and non-diagnostic measures of social anxiety, CSA, and history of suicide attempt as well as age

https://doi.org/10.1017/S0033291704002922 Published online by Cambridge University Press

of onset for these measures were also determined by computer algorithm.

Finally, standard measures of sociodemographic variables and rearing history were also obtained. Educational level was collapsed to a four-point scale: (1) those who left school early (before 10 years of schooling) without any further training; (2) those who had some high school education, a diploma, trade certificate, or apprenticeship; (3) those who attended a technical or teacher's college; and (4) those who had a university education or higher. Religion was divided into six categories: Roman Catholic, Anglican/Presbyterian/Uniting Church, Baptist/Methodist, Greek or Russian Orthodox, Other, and None. Church attendance was collapsed into a two-point scale: at least weekly *versus* less often. Zygosity of same-sex twin pairs was determined by standard questions for zygosity assignment (Nichols & Bilbro, 1966).

In Australia, minority populations differ considerably from those in the United States (less than 5%). No member of any minority was excluded from participation in the sample being analyzed; however, research on Australian aboriginal populations requires special community consultation procedures and permissions, and thus, this group was not represented in this Australian Twin Panel.

Data analysis

Descriptive analyses

Kaplan–Meier estimates of the lifetime prevalence of DSM-IV AD were computed by gender, as well as by co-twin's DSM-IV AD status, using six dummy variables (i.e. MZ co-twin AD, DZ male co-twin AD, DZ female co-twin AD, DZ female co-twin unaffected, DZ male co-twin unaffected, and MZ co-twin unaffected; cf. Heath *et al.* 1997*b*). The rationale behind this is that those with an MZ AD co-twin are at greater risk of becoming AD than those with a DZ AD co-twin and so on, with those at lowest risk being individuals who have an MZ unaffected co-twin.

Ages-of-onset of co-morbid diagnoses were elicited to determine how often the onset of AD occurred before, in the same year, or after the onset of a psychiatric disorder. The association between AD and sociodemographic and psychiatric predictors was then investigated using Cox regression models. The use of such models allowed us to correct for (i) censoring (the problem that some of the non-AD individuals in this young sample are not yet through the period of risk for AD), (ii) the fact that a disorder occurring after the onset of AD should not properly be included as a predictor, and (iii) the incorporation of time-dependent covariates, i.e. those that may change in value over the course of the observation period (e.g. because of onset of depression; Allison, 1995). Cox regression estimates a hazard ratio, which is the ratio of the estimated hazard (i.e. probability of onset of AD) for those with the covariate (e.g. DSM-IV depression) to those without the covariate. For these analyses, Anglican/Presbyterian/Uniting Church served as the reference group for the religion variables, and those who left school early with no further training were the reference group for the education measures. Where significant gender × predictor interactions were observed, separate measures were created for men and women. Both members of pairs were included in these regression analyses; therefore, confidence intervals were adjusted to allow for the non-independence of twin pairs using the Huber–White robust variance estimation option as implemented via the STATA statistical package (StataCorp, 1999). Models were re-estimated with inclusion of dummy variables for twin-pair zygosity (MZ *versus* DZ), having an AD MZ co-twin, and having an AD DZ co-twin, to determine whether increased risk was observed in the MZ compared to the DZ co-twins of AD twins after controlling for psychiatric and sociodemographic predictors. Inclusion of these dummy variables for twin-pair zygosity and AD history resulted in a violation of the assumption of proportional hazards, thus hazard ratios associated with these measures represent an average effect over the range of time (Allison, 1995). Alternative models explicitly allowing for the interaction of these zygosity measures with time (i.e. allowing for deviations from the assumption of proportional hazards; Allison, 1995) were also fitted to the data and yielded similar results to those obtained under the assumption of proportional hazards, hence we report findings under the model with no interactions. Differences in hazard ratios (MZ *versus* DZ) were tested by Wald χ^2 tests (adjusted for

non-independence of observations in twin pairs).

Genetic model-fitting

In order to determine the extent of genetic and environmental influences on risk of AD, genetic structural equation models were fitted to the twin data by the maximum-likelihood method using the Mx statistical modeling package (Neale *et al*. 1999). Normal liability threshold models were initially fitted to the data by the maximum-likelihood method. This model yielded estimates of the proportion of the total variance that could be explained by additive genetic (a^2), shared environmental (c^2), and non-shared environmental factors (e^2) without covariate adjustment. The full model allowed for genotype × gender interaction as well as different prevalence estimates (i.e. threshold values) for males and females in each of the zygosity groups. After confirming that there were no gender differences in genetic and environmental estimates ($\chi^2 = 0{\cdot}671$, df $= 2$, $p \geqslant 0{\cdot}50$), several submodels were fitted to the data to determine which prevalence estimates could be equated. From these submodels, it was determined that the best-fitting model was one in which all female prevalence estimates could be equated, MZ males had their own prevalence, and prevalence estimates for DZ males from both same-sex and opposite-sex pairs could be equated. Prescott *et al*. (1999) report a consistent finding of prevalence differences between MZ and DZ males in the Virginia Twin Study. Estimated additive genetic, shared environmental, and non-shared environmental variance components and their 95% likelihood-based confidence intervals (Neale & Miller, 1997) were recomputed under this model.

Based on the results of fitting Cox regression models, we subsequently modified this basic normal liability threshold model to control for significant ($p \leqslant 0{\cdot}05$) sociodemographic and psychiatric predictors. This was done by jointly modeling the probit regression of AD on these covariates and the genetic and environmental contributions to the residual variance in AD liability. Under the adjusted threshold model

$$t_i = \mu_t - \beta_1 \text{Depression} - \beta_2 \text{Conduct\_disorder} - \ldots - \beta_n x_n,$$

where t_i is the threshold for the ith individual, μ_t is the mean threshold, and $\beta_1, \ldots, \beta_n$ are probit regression coefficients which give the regressions of AD liability on significant sociodemographic and psychiatric predictors ($x_1, \ldots, x_n$). By doing this, we tested for residual genetic and environmental contributions to variation in risk of AD, controlling for the regression of AD risk on the covariates. For this analysis, covariates with an onset before or in the same year as the onset of AD were coded as 1 and those with onsets after the onset of AD were coded as 0. This coding scheme is conservative in that it will count as a predictor some cases where onset of AD occurred before, but during the same year as, onset of the second disorder. This over-correction should cause the magnitude of residual genetic influences on AD risk to be underestimated.

It has been hypothesized that measures of personality may be important mediators of genetic influences on alcoholism risk (Cloninger, 1987). Thus, the same set of analyses were repeated on a subsample of respondents (1238 twin pairs; Heath *et al*. 2001) who had completed a follow-up mailed questionnaire that included the Eysenck Personality Questionnaire (EPQ; Eysenck & Eysenck, 1976; Eaves *et al*. 1989) as well as additional personality data based on a short-form version of Cloninger's Tridimensional Personality Questionnaire (TPQ; Cloninger *et al*. 1991; Heath *et al*. 1994). Measures of Extraversion, Neuroticism, Social-Nonconformity ('Lie Scale'), Tough-Mindedness ('Psychoticism'), Novelty-Seeking, Harm Avoidance, and Reward Dependence were included as additional control variables in these analyses.

RESULTS

Participants in the present study ranged in age from 23 to 36 years, with an average age of 30 years. With regard to religion, 44·4% reported being raised in the Anglican/Presbyterian/Uniting churches, 30·3% reported Roman Catholic as their religion, 5·2% were Baptist/Methodist, 1·5% Orthodox, 7·2% Other, and 11·4% reported no religion. However, only 10% of the sample noted attending church at least once a week. The sample was relatively well educated, with 27·2% having a university education or

https://doi.org/10.1017/S0033291704002922 Published online by Cambridge University Press

Table 1. *Proportion of co-morbid diagnoses in which the onset of alcohol dependence (AD) occurred before, in the same year, or after the onset of a psychiatric predictor*

	% AD before		% AD same year		% AD after	
	Males	Females	Males	Females	Males	Females
DSM-IV						
Major depression	49·8	44·3	9·4	14·6	40·8	41·1
Conduct disorder	0·5	0·0	1·8	2·4	97·7	97·6
Panic disorder	36·4	48·0	9·1	8·0	54·6	44·0
Social anxiety problems	8·2	10·3	2·6	2·7	89·3	86·9
Suicide attempt	51·5	34·5	12·1	6·9	36·4	58·6
Childhood sexual abuse	0·0	0·7	0·0	5·0	100·0	94·3

greater, 29% with a technical or teacher's college certification, 34·7% with some high school with additional qualifications. Only 9·1% left school before 10 years and had no further training.

The onset of DSM-IV depression occurred with about equal frequency both before and after the onset of AD regardless of gender (Table 1). The onset of DSM-IV conduct disorder, CSA, and, to a lesser extent, the onset of social anxiety tended to occur before the onset of DSM-IV AD, with approximately 98% of both men and women reporting the onset of AD after the onset of conduct disorder, over 94% of men and women reporting the onset of AD after the onset of CSA, and about 88% of men and women reporting the onset of AD after the onset of social anxiety problems. Suicide attempt more often preceded the onset of AD in women, but followed the onset of AD in men.

Prevalence of AD

Consistent with previous reports (e.g. Teesson *et al*. 2000) showing higher 12-month prevalence of alcohol-use disorders in Australia than in the USA, this young adult Australian sample was a heavy-drinking cohort, with prevalence of lifetime abstinence less than 1% in both genders. A total of 89% of men reported drinking at least nine standard drinks, and 69% of women at least seven drinks in a single day on at least one occasion. The lifetime prevalence of AD by age 35 years was 34·3% in men and 17·0% for women (Fig. 1). Cumulative incidence of AD was subsequently examined as a function of co-twin's AD status. Lifetime prevalence by age 35 was 42·1% for women with an AD MZ co-twin, 28·5% for women with an AD DZ female co-twin and 21·1% for those with an affected DZ male co-twin (Fig. 2*a*). Prevalence rates were reduced in women with an unaffected DZ male or female co-twin (~15% by age 35) and even smaller in those women with an unaffected MZ co-twin (10·8%). A similar pattern of results was obtained for men although prevalence rates were higher in all cases relative to those obtained for women (Fig. 2*b*). Lifetime prevalence by age 35 was highest in men with an AD MZ co-twin (53·9%), lower in men with an AD female DZ co-twin (48·0%) and men with an AD DZ male co-twin (42·7%), lower in men who had an unaffected male or female DZ co-twin (32%) and lowest in men with an unaffected MZ co-twin (19·3%).

FIG. 1. Lifetime prevalence of DSM-IV alcohol dependence as a function of age, stratified by gender. –●–, Males; ···○···, females.

The risk for AD was increased in men and in Roman Catholics; however, there was a decreased risk in males who reported having a university education and in men and women with at least some high-school education with

https://doi.org/10.1017/S0033291704002922 Published online by Cambridge University Press

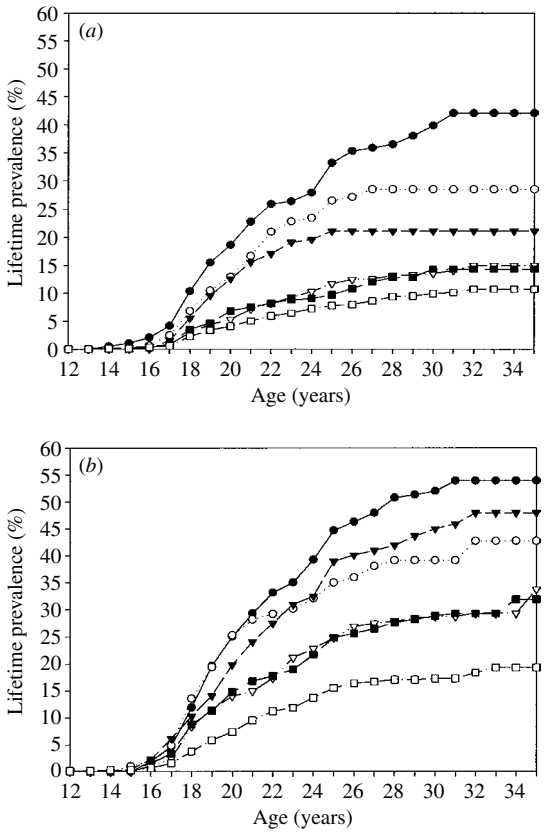

FIG. 2. Lifetime prevalence of DSM-IV alcohol dependence as a function of age and co-twin's alcohol dependence history in (*a*) women and (*b*) men. –●–, MZ co-twin alcohol dependent; ···○···, DZ male co-twin alcohol dependent; –▼–, DZ female co-twin alcohol dependent; –▽···, DZ female co-twin unaffected; –■–, DZ male co-twin unaffected; –□···, MZ co-twin unaffected.

Table 2. *Sociodemographic and psychiatric predictors of alcohol dependence. Hazard ratios estimated from Cox regression models*

	Hazard ratio	95% CI
Gender – Male	2·68**	2·27–3·16
Educational level†		
University-educated males	0·57**	0·44–0·73
University-educated females	0·87	0·66–1·14
At least some high school with a diploma or apprenticeship	0·81*	0·66–0·99
Technical or teacher's college	0·83	0·68–1·01
Religion†		
Roman Catholic	1·17*	1·01–1·35
Baptist/Methodist	0·73*	0·53–0·99
Orthodox	0·54*	0·30–0·97
Other	0·82	0·63–1·05
None	1·11	0·92–1·35
Church attendance	0·56**	0·43–0·73
Psychiatric history		
DSM-IV depression	1·52**	1·28–1·81
DSM-IV conduct disorder		
Males	1·95**	1·65–2·32
Females	2·40**	1·85–3·12
DSM-IV panic disorder	1·40	0·86–2·27
Social anxiety problems	1·16*	1·02–1·32
Suicide attempt		
Males	0·79	0·43–1·43
Females	1·58*	1·06–2·35
Childhood sexual abuse		
Males	1·23	0·91–1·65
Females	1·73**	1·38–2·17

* $p<0·05$, ** $p<0·01$.
† Reference group for education: those who left school early (before 10 years of schooling). Reference group for religion: Anglican/Presbyterian/Uniting Church.

further qualifications (Table 2). In addition, there was a decreased risk for AD in Baptists/Methodists, in those with an Orthodox religious affiliation, and in those who report attending church at least once a week. For the psychiatric disorders, it can be seen that those with a history of problems with social anxiety and DSM-IV major depression were at increased risk for AD. The strongest association with AD was with history of DSM-IV conduct disorder, both in men and especially in women. Finally, histories of suicide attempt and CSA were significant risk factors for AD in women but not in men.

Having an AD co-twin, whether it be MZ or DZ, was a significant and substantial risk factor for AD (Table 3). This effect was only modestly reduced when psychiatric and sociodemographic predictors were controlled for. Further, the hazard ratio for AD in the case of having an alcoholic MZ co-twin (21·44 without covariate adjustment, 18·26 after covariate adjustment) was almost twice that associated with having a DZ affected co-twin (11·45 and 10·98 respectively). This difference between MZ and DZ hazard ratios was significant both before and after covariate adjustment (Wald $\chi^2=12·24$, df=1, $p=0·0005$ and Wald $\chi^2=7·97$, df=1, $p=0·0048$ respectively). In analyses that also controlled for personality risk factors, those that scored in the highest quartile on Extraversion, Neuroticism, and Psychoticism were at significantly greater risk of AD, as were those that scored in the highest quartile on Novelty Seeking. However, controlling for personality differences, there still remained a significantly elevated risk to MZ co-twins of alcoholics compared to

https://doi.org/10.1017/S0033291704002922 Published online by Cambridge University Press

Table 3. *Hazard ratios estimated from Cox regression models for MZ and DZ twins both before and after controlling for sociodemographic and psychiatric predictors*

	Before controlling for predictors		After controlling for predictors	
	Hazard ratio	95% CI	Hazard ratio	95% CI
Having an MZ co-twin who is alcohol dependent	21·44**	16·26–28·27	18·26**	13·69–24·36
Having a DZ co-twin who is alcohol dependent	11·45**	9·01–14·55	10·98**	8·72–13·82

** $p<0{\cdot}01$.

Table 4. *Twin correlations (and 95% CI) and genetic and environmental variance component estimates (and 95% CI) for DSM-IV alcohol dependence before and after controlling for covariates*

	Before controlling for covariates	After controlling for covariates
MZF	0·53 (0·39–0·66)	0·47 (0·32–0·61)
MZM	0·59 (0·52–0·66)	0·48 (0·36–0·59)
DZF	0·28 (0·10–0·45)	0·22 (0·03–0·40)
DZM	0·26 (0·10–0·41)	0·24 (0·07–0·40)
DZOS	0·19 (0·04–0·33)	0·14 (−0·02–0·29)
a^2	0·53 (0·33–0·61)	0·47 (0·28–0·55)
c^2	0·00 (0·00–0·15)	0·00 (0·00–0·14)
e^2	0·47 (0·39–0·56)	0·53 (0·45–0·63)

DZ co-twins [MZ hazard ratio (HR) 18·49, 95% CI 13·96–24·50; DZ HR 11·80, 95% CI 9·40–14·82). The fact that this difference remained after controlling for other predictors suggests that much of the genetic influence on the risk for AD remains unexplained and is not associated with religion, church attendance, education, history of major depression, conduct disorder, panic disorder, suicide attempt, or CSA.

Genetic model-fitting

Table 4 shows twin correlations both before and after controlling for significant covariates. The parameter estimates obtained from fitting the unadjusted and covariate-adjusted genetic and environmental models to the AD data (also shown in Table 4) confirm significant genetic influences on AD both before and after controlling for the effects of sociodemographic and psychiatric predictors ($a^2=0{\cdot}53$, 95% CI 0·33–0·61 and $a^2=0{\cdot}47$, 95% CI 0·28–0·55 respectively). The substantial residual heritability that is observed implies that these sociodemographic and psychiatric risk factors play at most a minor role as mediators of genetic risk for AD. No significant shared environmental influence on risk of AD was found ($c^2=0{\cdot}00$ in both models). Finally, non-shared environmental factors accounted for about 50% of the total variance in alcoholism liability both before and after controlling for sociodemographic and psychiatric predictors. The adjusted heritability estimate of AD after controlling for personality as well as psychiatric and sociodemographic predictors, again remained substantial (45%, 95% CI 26–54) suggesting that not much of the genetic influence on the risk for AD is accounted for by these personality measures. Shared environmental effects were again estimated at 0% and non-shared environmental influences accounted for 55% (95% CI 46–65) of the residual variance of AD.

DISCUSSION

Results indicated that about half of the variance in DSM-IV AD risk was attributable to genetic factors. Additional analyses (not shown) indicated that this result was not conditional on the similarity of twins' early experiences (e.g. being in the same classroom or having the same friends). Consistent with findings from an older cohort of Australian twins (Heath *et al.* 1997*b*), we also found no significant differences in heritability in males and females. These results, however, do not support those of Prescott *et al.* (1999), who found sex differences in estimates of heritability for multiple measures of alcohol abuse and dependence in a large

https://doi.org/10.1017/S0033291704002922 Published online by Cambridge University Press

population-based sample of southern USA (Virginia) twin pairs, indicating limitations in generalizing results between southern USA and Australian based samples. Also in agreement with findings from other samples, there were large differences in rates of AD in men and women, with men and women having lifetime prevalence rates of approximately 35% and 17%. Women with the same degree of genetic risk as men were less likely to become alcoholic, as can be seen by comparing the rate of women *versus* men with an AD DZ male co-twin or DZ female co-twin (Fig. 2*a*, *b*).

Results from the Cox regression models suggest that major depression, social anxiety problems, conduct disorder, and suicide attempt (in women only) may be significant mediators of genetic influences on alcoholism risk. Similar to previous reports (e.g. Prescott *et al.* 1997), we also found that high Extraversion, Neuroticism, Psychoticism, and Novelty Seeking scores were associated with increased risk of AD. However, controlling for these significant risk factors did not remove the significant association with having an alcoholic MZ co-twin, and the adjusted estimate of heritability of AD remained substantial suggesting that much of the genetic influence on the risk for AD is not accounted for by these psychiatric and personality measures. Thus, while history of conduct disorder and associated personality traits (Slutske *et al.* 1998, 2002; Fu *et al.* 2002), as well as major depression (Kendler *et al.* 1993; Prescott *et al.* 2000) may be important *genetic correlates* of AD risk, they appear not to be important mediators of genetic influences on risk (i.e. much of the association may be indirect).

In addition to investigating psychiatric risk factors for AD, we also assessed the potentially important contribution of sociodemographic variables, such as religiosity. In this sample, as in the older cohort analyzed by Heath *et al.* (1997*b*), Roman Catholicism was associated with increased alcoholism risk. We cannot exclude the possibility that this association is due to differences in ancestral origin (i.e. Australians of Irish ancestry), which may reflect underlying genetic differences. Those reporting Baptist/Methodist and Orthodox religious beliefs were at a decreased risk for alcoholism. In addition, regular church attendance was associated with decreased risk for AD. As with Heath *et al.* (1997*b*), we cannot exclude the possibility that drinking patterns affect church attendance. Educational level, which may in part be genetically influenced, was a significant protective factor in most cases. Despite these significant associations with AD, genetic model fitting failed to find significant shared environmental effects on the risk for alcoholism. Both before and after controlling for significant psychiatric and sociodemographic predictors, shared environmental effects were estimated at 0% with 95% confidence intervals of 0–15. This finding does not, however, preclude important genotype × shared environment interaction effects, whereby the environmental effects of family background risk factors are dependent upon offspring genetic vulnerabilities, since such G × E effects are confounded with additive genetic effects in twin data (Heath *et al.* 2002). It is also possible that genetic non-additivity (dominance or epistasis) is masking a modest effect of shared environment (Neale & Cardon, 1992).

Several important limitations need to be considered with interpreting these results. First, in controlling for psychiatric risk factors, we assumed that it was the occurrence of psychiatric disorder (e.g. onset of major depression) rather than subclinical manifestations (e.g. first depressive symptoms) that was associated with increased risk of AD. While this assumption is used routinely in epidemiological studies, it could cause underestimation of the importance of our control variables in accounting for genetic influences on AD risk. Second, we are also dependent upon the accuracy of retrospective reporting, so that errors in remembering whether a disorder had occurred, or when its onset had occurred, could have caused us to underestimate the importance of such risk factors. Since controlling for the lifetime occurrence of other psychiatric disorders only modestly diminished the residual heritability of AD, bias in recall of timing of onset of other disorders in unlikely to be an important factor. Some disorders that were not assessed in this study (e.g. post-traumatic stress disorder) but are associated with AD (Kessler *et al.* 1997) may play some role in the inheritance of AD risk. Since we did not assess ASPD, we cannot preclude the possibility that it is a major mediator of genetic influences on AD risk, although the low prevalence of the disorder, particularly in women,

and the fact that ASPD can only be diagnosed in those with a history of conduct disorder, makes it unlikely that it will account for much of the unexplained genetic variance in AD risk. Thirdly, these analyses included only co-morbid conditions (e.g. major depression) with onset prior to, or in the same year as, onset of AD. While there are instances where individuals report onset of AD before onset of other psychiatric outcomes, there are also undoubtedly cases where onset of co-morbid conditions has not yet occurred at the time of interview. It is possible that a genetic vulnerability for major depression (for example) increases risk for AD regardless of whether onset of depression occurs before or after onset of AD; thus, our analyses provide conservative estimates of the amount of variation of AD liability accounted for by these psychiatric measures.

With this Australian sample, results can only be generalized to individuals of European ancestry. Moreover, this twin panel, being a volunteer panel, was not systematically ascertained from birth records and well-educated individuals may be over-represented. We also cannot exclude the possibility that systematic sampling biases have occurred with respect to other, unmeasured variables that might be important determinants of alcoholism risk (Heath *et al.* 1997*b*). Finally, the Australian twin panel is a general population sample rather than clinically ascertained. Thus, the majority of cases of alcoholism are mild and typically untreated so results cannot be generalized to more severe alcoholics.

In general, results from the present set of analyses are consistent with an important genetic influence on risk of developing alcoholism in both men and women. However, the way these genetic influences arise remains unclear. Perhaps, as in Asian populations (cf. Higuchi *et al.* 1994, 1996*a*, *b*), genes that directly affect alcohol metabolism, or genes that affect other aspects of alcohol's effects (e.g. subjective intoxication or ataxia; Schuckit & Smith, 1996; Heath *et al.* 1999) play a more important role in the etiology of AD than has previously been suspected. Further exploration into this topic, using additional information on alcohol use, subjective reactions, or levels of consumption, is needed to clarify the pathways through which genetic factors influence AD.

ACKNOWLEDGEMENTS

This work supported by NIH grants: AA11998, AA10249, AA0758O, DA12854, AA13321.

DECLARATION OF INTEREST

None.

REFERENCES

Allison, P. D. (1995). *Survival Analysis using the SAS System: A Practical Guide*. SAS Institute Inc. Cary, NC.

APA (1994). *Diagnostic and Statistical Manual of Mental Disorders* (4th edn). American Psychiatric Association: Washington, DC.

Bierut, L. J., Heath, A. C., Bucholz, K. K., Dinwiddie, S. H., Madden, P. A. F., Statham, D. J., Dunne, M. P. & Martin, N. G. (1999). Major depressive disorder in a community-based twin sample: are there different genetic and environmental contributions for men and women? *Archives of General Psychiatry* **56**, 557–563.

Bucholz, K. K., Cadoret, R., Cloninger, C. R., Dinwiddie, S. H., Hesselbrock, V. M., Nurnberger, J. I., Reich, T., Schmidt, I. & Schuckit, M. A. (1994). A new, semi-structured psychiatric interview for use in genetic linkage studies: a report on the reliability of the SSAGA. *Journal of Studies on Alcohol* **55**, 149–158.

Bucholz, K. K., Heath, A. C. & Madden, P. A. F. (2000). Transitions in drinking in Adolescent females: evidence from the Missouri Adolescent Female Twin Study. *Alcoholism: Clinical and Experimental Research* **24**, 914–923.

Cadoret, R. J. (1994). Genetic and environmental contributions to heterogeneity in alcoholism: findings from the Iowa adoption studies. *Annals of the New York Academy of Science* **708**, 59–71.

Cadoret, R. J., Cain, C. A., Troughton, E. & Heywood, E. (1985*a*). Alcoholism and antisocial personality: interrelationships, genetic and environmental factors. *Archives of General Psychiatry* **42**, 161–167.

Cadoret, R. J., O'Gorman, T. W., Heywood, E. & Troughton, E. (1985*b*). Genetic and environmental factors in major depression. *Journal of Affective Disorders* **9**, 155–164.

Cadoret, R. J., Troughton, E. & O'Gorman, T. W. (1987). Genetic and environmental factors in alcohol abuse and antisocial personality. *Journal of Studies on Alcohol* **48**, 1–8.

Cloninger, C. R. (1987). Neurogenetic adaptive mechanisms in alcoholism. *Science* **236**, 410–416.

Cloninger, C. R., Bohman, M. & Sigvardsson, S. (1981). Inheritance of alcohol abuse: cross-fostering analysis of adopted men. *Archives of General Psychiatry* **38**, 861–868.

Cloninger, C. R. & Gottesman, I. I. (1987). Genetic and environmental factors in antisocial behavior disorder. In *The Causes of Crime: New Biological Approaches* (ed. S. A. Mednick, T. E. Moffitt and S. A. Stack), pp. 92–109. Cambridge University Press: New York.

Cloninger, C. R., Przybeck, T. R. & Svrakic, D. M. (1991). The tridimensional personality questionnaire: U.S. normative data. *Psychological Report* **69**, 1047–1057.

Eaves, L. J., Eysenck, H. J. & Martin, N. G. (1989). *Genes, Culture, and Personality: An Empirical Approach*. Academic Press: London.

Eysenck, H. J. & Eysenck, S. B. G. (1976). *Psychoticism as a Dimension of Personality*. Hodder and Stoughton: London.

Fergusson, D. M., Horwood, L. J. & Lynskey, M. T. (1996). Childhood sexual abuse and psychiatric disorder in young adulthood, II: psychiatric outcomes of childhood sexual abuse. *Journal of the American Academy of Child and Adolescent Psychiatry* **35**, 1365–1374.

Fu, Q., Heath, A. C., Bucholz, K. K., Nelson, E. C., Goldberg, J., Lyons, M. J., True, W. R., Jacob, T., Tsuang, M. T. & Eisen, S. A. (2002). Shared genetic risk of major depression, alcohol dependence and marijuana dependence: the contribution of antisocial personality disorder in men. *Archives of General Psychiatry* **59**, 1125–1132.

Goodwin, D. W., Schulsinger, F., Hermansen, L., Guze, S. B. & Winokur, G. (1972). Alcohol problems in adoptees raised apart from alcoholic biologic parents. *Archives of General Psychiatry* **28**, 238–255.

Goodwin, D. W., Schulsinger, F., Knop, J., Mednick, S. & Guze, S. B. (1977). Alcoholism and depression in adopted-out daughters of alcoholics. *Archives of General Psychiatry* **34**, 751–755.

Heath, A. C. (1995). Genetic influences on alcoholism risk? A review of adoption and twin studies. *Alcohol Health and Research World* **19**, 166–171.

Heath, A. C., Berg, K., Eaves, L. J., Solaas, M. H., Corey, L. A., Sundet, H. M., Magnus, P. & Nance, W. E. (1985). Education policy and the heritability of educational attainment. *Nature* **314**, 734–736.

Heath, A. C., Bucholz, K. K., Madden, P. A. F., Dinwiddie, S. H., Slutske, W. S., Beirut, L. J., Statham, D. J., Dunne, M. P., Whitfield, J. & Martin, N. G. (1997*b*). Genetic and environmental contributions to alcohol dependence risk in a national twin sample: consistency of findings in women and men. *Psychological Medicine* **27**, 1381–1396.

Heath, A. C., Cloninger, C. R. & Martin, N. G. (1994). Testing a model for the genetic structure of personality: a comparison of the personality systems of Cloninger and Eysenck. *Journal of Personality and Social Psychology* **66**, 762–775.

Heath, A. C., Howells, W., Madden, P. A. F., Bucholz, K. K., Nelson, E. C., Slutske, W. S., Statham, D. J., Kirk, K. & Martin, N. G. (2001). Predictors of non-response to a questionnaire survey of a volunteer twin panel: findings from the Australian 1989 twin cohort. *Twin Research* **4**, 73–80.

Heath, A. C., Madden, P. A. F., Bucholz, K. K., Dinwiddie, S. H., Slutske, W. S., Bierut, L. J., Rohrbaugh, J. W., Statham, D. J., Dunne, M. P., Whitfield, J. B. & Martin, N. G. (1999). Genetic differences in alcohol sensitivity and the inheritance of alcoholism risk. *Psychological Medicine* **29**, 1069–1081.

Heath, A. C., Slutske, W. S. & Madden, P. A. F. (1997*a*). Gender differences in the genetic contribution to alcoholism risk and to alcohol consumption patterns. In *Gender and Alcohol* (ed. R. W. Wilsnack and S. C. Wilsnack), pp. 114–149. Rutgers University Press: Rutgers, NJ.

Heath, A. C., Todorov, A. A., Nelson, E. C., Madden, P. A. F., Bucholz, K. K. & Martin, N. G. (2002). Gene-environment interaction effects on behavioral variation and risk of complex disorders: the example of alcoholism and other psychiatric disorders. *Twin Research* **5**, 30–43.

Hesselbrock, M., Easton, C., Bucholz, K. K., Schuckit, M. & Hesselbrock, V. (1999). A validity study of the SSAGA – a comparison with the SCAN. *Addiction* **94**, 1361–1370.

Higuchi, S., Matsushita, S., Imazeki, H., Kinoshita, T., Takagi, S. & Kono, H. (1994). Aldehyde dehydrogenase genotypes in Japanese alcoholics. *Lancet* **343**, 741–742.

Higuchi, S., Matsushita, S., Muramatsu, T., Murayama, M. & Hayashida, M. (1996*a*). Alcohol and aldehyde dehydrogenase genotypes and drinking behavior in Japanese. *Alcoholism: Clinical and Experimental Research* **20**, 493–497.

Higuchi, S., Muramatsu, T., Matsushida, S., Murayama, M. & Hayashida, M. (1996*b*). Polymorphisms of ethanol-oxidizing enzymes in alcoholics with inactive ALDH2. *Human Genetics* **97**, 431–434.

Hrubec, Z. & Omenn, G. S. (1981). Evidence of genetic predisposition to alcoholic cirrhosis and psychosis: twin concordances for alcoholism and its biological points of zygosity among male veterans. *Alcoholism: Clinical and Experimental Research* **5**, 207–215.

Jacobson, K. C., Neale, M. C., Prescott, C. A. & Kendler, K. S. (2000). Cohort differences in genetic and environmental influences on retrospective reports of conduct disorder among male twins. *Psychological Medicine* **30**, 775–787.

Kendler, K. S., Bulik, C. M., Silberg, J., Hettema, J. M., Myers, J. & Prescott, C. A. (2000). Childhood sexual abuse and adult psychiatric and substance use disorders in women: an epidemiological and cotwin control analysis. *Archives of General Psychiatry* **57**, 953–959.

Kendler, K. S., Gardner, C. O. & Prescott, C. A. (1997*a*). Religion, psychopathology, and substance use and abuse: a multimeasure, genetic-epidemiologic study. *American Journal of Psychiatry* **154**, 322–329.

Kendler, K. S., Heath, A. C., Neale, M. C., Kessler, R. C. & Eaves, L. J. (1992*a*). A population-based twin study of alcoholism in women. *Journal of the American Medical Association* **268**, 1877–1882.

Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C. & Eaves, L. (1992*b*). A population-based twin study of major depression in women: the impact of varying definitions of illness. *Archives of General Psychiatry* **49**, 257–266.

Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C. & Eaves, L. J. (1993). A test of the equal-environment assumption in twin studies of psychiatric illness. *Behavior Genetics* **23**, 21–27.

Kendler, K. S. & Prescott, C. A. (1999). A population-based twin study of lifetime major depression in men and women. *Archives of General Psychiatry* **56**, 39–44.

Kendler, K. S., Prescott, C. A., Neale, M. C. & Perderson, N. L. (1997*b*). Temperance board registration for alcohol abuse in a national sample of Swedish male twins, born 1902–1949. *Archives of General Psychiatry* **54**, 178–184.

Kendler, K. S., Walters, E. E., Neale, M. C., Kessler, R. C., Heath, A. C. & Eaves, L. J. (1995). The structure of genetic and environmental risk factors for six major psychiatric disorders in women: phobia, generalized anxiety disorder, panic diorder, bulimia, major depression and alcoholism. *Archives of General Psychiatry* **52**, 374–383.

Kessler, R. C., Crun, R. M., Warner, L. A., Nelson, C. B., Schulenberg, J. & Anthony, J. C. (1997). Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. *Archives of General Psychiatry* **54**, 313–321.

Koskenvuo, M., Langinvainio, J., Kaprio, J., Lonnquist, J. & Tienari, P. (1984). Psychiatric hospitalization in twins. *Acta Genetica Medicae et Gemellolgiae* **33**, 321–332.

Lyons, M. J., Eisen, S. A., Goldberg, J., True, W., Lin, N., Meyer, J. M., Toomey, R., Faraone, S. V., Merla-Ramos, M. & Tsuang, M. T. (1998). A registry-based twin study of depression in men. *Archives of General Psychiatry* **55**, 468–472.

Lyons, M. J., True, W. R., Eisen, S. A., Goldberg, J., Meyer, J. M., Faraone, S. V., Eaves, L. J. & Tsuang, M. T. (1995). Differential heritability of adult and juvenile antisocial traits. *Archives of General Psychiatry* **52**, 906–915.

McGue, M. (1994). Genes, environment and the etiology of alcoholism. In *The Development of Alcohol Problems: Exploring the Biopsychosocial Matrix of Risk* (ed. R. Zucker, G. Boyd and J. Howard), pp. 1–40. US Department of Health and Human Services: Rockville, MD.

Merikangas, K. R. (1990). The genetic epidemiology of alcoholism. *Psychologica Medicine* **20**, 11–22.

Merikangas, K. R. & Avenevoli, S. (2000). Implications of genetic epidemiology for the prevention of substance use disorders. *Addictive Behaviors* **25**, 807–820.

Merikangas, K. R., Stolar, M., Stevens, D. E., Goulet, J., Preisig, M. A., Fenton, B., Zhang, H., O'Malley, S. S. & Rounsaville, B. J. (1998). Familial transmission of substance use disorders. *Archives of General Psychiatry* **55**, 973–979.

Neale, M. C., Boker, S. M., Xie, G. & Maes, H. H. (1999). *MX: Statistical Modeling* (5th edn). Department of Psychiatry, Virginia Commonwealth University: Richmond, VA.

Neale, M. C. & Cardon, L. R. (1992). *Methodology for Genetic Studies of Twins and Families*. Kluwer Academic Publishers: Dordrecht.

Neale, M. C. & Miller, M. B. (1997). The use of likelihood-based confidence intervals in genetic models. *Behavior Genetics* **27**, 113–120.

Nelson, E. C., Heath, A. C., Madden, P. A. F., Cooper, M. L., Dinwiddie, S. H., Bucholz, K. K., Glowinski, A., McLaughlin, T., Dunne, M. P., Statham, D. J. & Martin, N. G. (2002). Association between self-reported childhood sexual abuse and adverse psychosocial outcomes. *Archives of General Psychiatry* **59**, 139–145.

Nichols, R. C. & Bilbro, W. C. (1966) .The diagnosis of twin zygosity. *Acta Genetica et Statistica Medica* **16**, 265–275.

Pickens, R. W., Svikis, D. S., McGue, M., Lykken, D. T., Heston, L. L. & Clayton, P. J. (1991). Heterogeneity in the inheritance of alcoholism: a study of male and female twins. *Archives of General Psychiatry* **48**, 19–28.

Prescott, C. A., Aggen, S. H. & Kendler, K. S. (1999). Sex differences in the sources of liability to alcohol abuse and dependence in a population-based sample of U.S. twins. *Alcoholism: Clinical and Experimental Research* **23**, 1136–1144.

Prescott, C. A., Aggen, S. H. & Kendler, K. S. (2000). Sex-specific genetic influences on the comorbidity of alcoholism and major depression in a population-based sample of U.S. twins. *Archives of General Psychiatry* **57**, 803–811.

Prescott, C. A., Neale, M. C., Corey, L. A. & Kendler, K. S. (1997). Predictors of problem drinking and alcohol dependence in a population-based sample of female twins. *Journal of Studies on Alcohol* **58**, 167–181.

Regier, D. A., Farmer, M. E., Rae, D. S., Locke, B. Z., Keith, S. J., Judd, L. L. & Goodwin, F. K. (1990). Comorbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiologic Catchment Area (ECA) study. *Journal of the American Medical Association* **26**, 2511–2518.

Reich, T., Cloninger, C. R., Van Eerdewegh, P., Rice, J. P. & Mullaney, J. (1988). Secular trends in the familial transmission of alcoholism. *Alcoholism: Clinical and Experimental Research* **12**, 458–464.

Romanov, K., Kaprio, J. & Rose, R. J. (1991). Genetics of alcoholism: effects of migration on concordance rates among male twins. *Alcohol and Alcoholism* **1** (Suppl.), 137–140.

Schuckit, M. A. & Smith, T. (1996). An 8-year follow-up of 450 sons of alcoholic and control subjects. *Archives of General Psychiatry* **53**, 202–210.

Sher, K. J., Walitzer, K. S., Wood, P. K. & Brent, E. E. (1991). Characteristics of children of alcoholics: putative risk factors, substance use and abuse, and psychopathology. *Journal of Abnormal Psychology* **100**, 427–448.

Sigvardsson, S., Bohman, M. & Cloninger, C. R. (1996). Replication of the Stockholm Adoption Study of Alcoholism: confirmatory cross-fostering analysis. *Archives of General Psychiatry* **53**, 681–687.

Slutske, W. S., Heath, A. C., Dinwiddie, S. H., Madden, P. A. F., Bucholz, K. K., Dunne, M. P., Statham, D. J. & Martin, N. G. (1997). Modeling genetic and environmental influences in the etiology of conduct disorder: a study of 2682 adult twin pairs. *Journal of Abnormal Psychology* **106**, 266–279.

Slutske, W. S., Heath, A. C., Dinwiddie, S. H., Madden, P. A. F., Bucholz, K. K., Dunne, M. P., Statham, D. J. & Martin, N. G. (1998). Common genetic risk-factors for conduct disorder and alcohol dependence. *Journal of Abnormal Psychology* **107**, 363–374.

Slutske, W. S., Heath, A. C., Madden, P. A. F., Bucholz, K. K., Statham, D. J. & Martin, N. G. (2002). Personality and the genetic risk for alcohol dependence. *Journal of Abnormal Psychology* **111**, 124–133.

Spak, L., Spak, F. & Allbeck, P. (1998). Sexual abuse and alcoholism in a female population. *Addiction* **93**, 1365–1373.

StataCorp (1999). *STATA Statistical Software, Release 6.0*. Stata Corporation: College Station, TX.

Teesson, M., Hall, W., Lynskey, M. & Degenhardt, L. (2000). Alcohol- and drug-use Disorders in Australia: implications from the National Survey of Mental Health and Wellbeing. *Australian and New Zealand Journal of Psychiatry* **34**, 206–213.

True, W. R., Xian, J., Scherrer, J. F., Madden, P. A. F., Bucholz, K. K., Heath, A. C., Eisen, S. A., Lyons, M. J., Goldberg, J. & Tsuang, M. T. (1999). Common genetic vulnerability for nicotine and alcohol dependence in men. *Archives of General Psychiatry* **56**, 655–661.