

The heritability of alcohol use disorders: a meta-analysis of twin and adoption studies

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Background. To clarify the role of genetic and environmental risk factors in alcohol use disorders (AUDs), we performed a meta-analysis of twin and adoption studies and explored the impact of sex, assessment method (interview *v.* hospital/population records), and study design (twin *v.* adoption study) on heritability estimates.

Method. The literature was searched for all unique twin and adoption studies of AUD and identified 12 twin and five adoption studies. The data were then reconstructed and analyzed using ordinal data full information maximum likelihood in the OpenMx program. Heterogeneity was tested with likelihood ratio tests by equating the parameters across studies.

Results. There was no evidence for heterogeneity by study design, sex or assessment method. The best-fit estimate of the heritability of AUD was 0.49 [95% confidence interval (CI) 0.43–0.53], and the proportion of shared environmental variance was 0.10 (95% CI 0.03–0.16). Estimates of unique environmental proportions of variance differed significantly across studies.

Conclusions. AUD is approximately 50% heritable. The multiple genetically informative studies of this syndrome have produced consistent results that support the validity of this heritability estimate, especially given the different potential methodological weaknesses of twin and adoption designs, and of assessments of AUD based on personal interviews *v.* official records. We also found evidence for modest shared environmental effects suggesting that environmental factors also contribute to the familial aggregation of AUDs.

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Introduction

Alcohol use disorder (AUD) is among the most common of psychiatric syndromes (Grant, 1997) and is often accompanied by significant psychosocial dysfunction, a range of medical co-morbidities and substantially increased mortality (Secretary of Health and Human Services, 1997). It has been known since classical times that AUD is familial (Bynum, 1984) and this has been verified by more modern family studies (Cotton, 1979). Since 1960, a series of twin (Kaij, 1960; McGue *et al.* 1992; Reed *et al.* 1996; Heath *et al.* 1997; Prescott *et al.* 1999; True *et al.* 1999; Knopik *et al.* 2004; Magnusson *et al.* 2012) and adoption (Goodwin *et al.* 1973, 1977; Bohman *et al.* 1981; Cloninger *et al.* 1981; Cadoret *et al.* 1987; Sigvardsson *et al.* 1996) studies have attempted to determine the relative roles of genetic and environmental factors in

the etiology of AUD. While these studies have been reviewed qualitatively several times (e.g. Heath, 1995; Prescott & Kendler, 1995; Dick & Bierut, 2006), we are unaware of any quantitative meta-analysis.

In addition to providing a more reliable estimate of the heritability of AUD, such an analysis could address four additional important questions. First, several early twin and adoption studies suggested that there were quantitative sex effects in the genetic factors for AUD – that genetic effects were stronger in males than in females (Goodwin *et al.* 1973; Bohman *et al.* 1981; McGue *et al.* 1992). The studies that found differential genetic effects as a function of sex, however, often relied on small samples, especially of females. Most recent, larger studies have been unable to detect genetic differences between the sexes. Accordingly, a quantitative meta-analysis of a now larger body of studies would more accurately evaluate this hypothesis.

Relatedly, five twin studies presented results on resemblance for AUDs in opposite-sex dizygotic (DZ) twin pairs and thus were able to test for the presence of qualitative sex effects for AUDs – that the genetic risk factors were not entirely the same in males and

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females. This is detected largely by comparing the magnitude of the correlation in same- *v.* opposite-sex DZ pairs. One study found evidence for such an effect for AUDs (Prescott *et al.* 1999), two did not (Heath *et al.* 1997; Magnusson *et al.* 2012), and two did not test for it (Caldwell & Gottesman, 1991; Knopik *et al.* 2004). Because qualitative sex effects can only be detected reliably with large samples (Prescott & Gottesman, 1993), meta-analytical methods provide an ideal procedure to evaluate evidence for this effect.

Second, some twin studies suggest that shared environmental risk factors contribute to the familial aggregation of AUDs (McGue *et al.* 1992; Kendler *et al.* 1997) while others do not (Heath *et al.* 1997; Prescott *et al.* 1999). The magnitude of the shared environmental variance, however, is typically small (but see Kaij, 1960 for an exception). In the presence of substantial genetic influences, quite large samples of twins are needed to detect shared environmental effects (Neale *et al.* 1994). A large meta-analysis would be much better powered to identify shared environmental effects for AUDs than an individual study, if indeed they are present.

Third, these studies utilized two different methods of assessment. A number of the twin and adoption studies utilized personal interviews, an approach that requires cooperation and relies critically on the accuracy of retrospective reporting of symptoms generally seen as socially undesirable (e.g. Cadoret *et al.* 1987; Reed *et al.* 1996; Prescott *et al.* 1999; True *et al.* 1999). Other studies utilized registry information, particularly from medical (Reed *et al.* 1996) and temperance board records (Cloninger *et al.* 1981; Kendler *et al.* 1997). This approach typically provides contemporaneously recorded information and requires no cooperation, but might have limited sensitivity and specificity in the detection of AUD as they require affected individuals to be detected with alcohol-related problems by the medical or legal system. While both official registrations – typically from medical and/or legal records – and clinical diagnoses are commonly used assessments of AUD, it is possible that the cases diagnosed by different assessment methods could reflect partly independent latent genetic factors. If the reliability of AUD diagnoses differed with these two methods, it could be reflected in additive genetic, shared and individual specific environmental variance components, because unreliability increases specific environmental variance thereby decreasing the proportion of variance due to other components.

Finally, twin and adoption studies are quite different in their assumptions and potential biases. The estimation of genetic effects in these two kinds of studies derives from quite distinct kinds of relationships: monozygotic (MZ) *v.* DZ twins, and biological and

adoptive relatives, respectively. Specifically, twin studies leverage the differential genetic relatedness between MZ and DZ twins with the major assumption that the rearing environments to which they are exposed are equally correlated. By contrast, adoption studies leverage the genetic or environmental similarity between biological or adoptive relatives with the major methodological concern being assortative placement – whether adoptees are placed randomly within adoptive homes. While there are many types of adoption designs, the literature on AUD has focused on the relationship between biological parents and their adopted away offspring. Previous research in other behavioral domains has suggested that estimates of genetic factors from adoption studies are smaller than the same estimates in twin studies (Loehlin, 1992; Rhee & Waldman, 2002). Would the estimated heritability of AUD from these two methods be similar?

In this paper, we perform a quantitative meta-analysis of all available twin and adoption studies of AUD and address these and other questions of interest.

Method

We searched PubMed and Google Scholar[®] for all twin and adoption studies of AUD. In addition, we searched the bibliographies of all of the relevant studies to further add samples to our analysis. To ensure completeness, we followed up by contacting leading researchers in the AUD genetics field. Studies were included in our analyses if they: (i) examined AUD, here defined as a syndrome including heavy alcohol use with significant adverse social, psychological and/or medical consequences, a definition broadly similar to the DSM-IV concepts of alcohol abuse or dependence (APA, 1994); and (ii) presented sufficient data to permit re-analysis. In practice, across the various studies, AUD was defined by clinical interview, hospital record diagnosis or temperance board registration. If multiple studies were published using the same data, we used the report with the largest sample size. Because these studies utilized a variety of different analytic approaches, it was necessary to reconstruct the data for each study. The features of the available twin and adoption studies are listed in Tables 1 and 2, respectively. Importantly, because we focused exclusively on AUD, twin studies examining only drinking frequency or quantity were omitted.

Most of the original twin studies used a model-fitting approach whereby non-significant parameters were sequentially dropped from the model. In such cases, it is standard practice to present reduced models with only the significant parameters. Accordingly, the model parameters that are reported

Table 1. Twin studies of alcohol abuse and dependence

Author (year)	Ascertainment	Assessment	Diagnostic measure	Country	N	Sex	Data
Included							
Kaij (1960)	Twin registry	Temperance board	Registration	Sweden	1 216	M	Tetrachoric
Gurling <i>et al.</i> (1984)	Clinical	Interview	ICD ^a	England	735	M & F	Contingency tables
Allgulander <i>et al.</i> (1991)	Twin registry	Hospital discharge	ICD ^b	Sweden	12 884	M & F	Tetrachoric
Romanov <i>et al.</i> (1991)	Twin registry	Hospital discharge	ICD-8 ^c	Finland	5 340	M & F ^d	Contingency tables
Caldwell & Gottesman (1991) ^e	Clinical	Interview	DSM-III	USA	154	M & F	Odds ratios
McGue <i>et al.</i> (1992)	Clinical	Interview	DSM-III	USA	258	M & F	Tetrachoric
Reed <i>et al.</i> (1996)	Twin registry	Registry	ICD-8 ^f	USA	26 974	M	Tetrachoric
Heath <i>et al.</i> (1997)	Twin registry	Interview	DSM III-R	Australia	5 889	M & F	Tetrachoric
Kendler <i>et al.</i> (1997)	Twin registry	Temperance board	Registration	Sweden	7 790	M	Tetrachoric
True <i>et al.</i> (1999)	Twin registry	Interview	DSM III-R	USA	2 364	M	Tetrachoric
Prescott <i>et al.</i> (1999)	Twin registry	Interview	DSM-IV	USA	9 259	M	Tetrachoric
Magnusson <i>et al.</i> (2012)	Twin registry	Interview/questionnaire	DSM-IV	Sweden	24 119	M & F	Tetrachoric
Excluded							
Hrubec & Omenn (1981)	VA medical records		VA medical records	USA	15 924	M	Included in Reed <i>et al.</i> (1996)
Pickens <i>et al.</i> (1991)	Clinical		DSM-III	USA	338	M & F	Included in McGue <i>et al.</i> (1992)
Kendler <i>et al.</i> (1992)	Population		DSM III-R	USA	2 060	F	Included in Prescott <i>et al.</i> (1999)
Prescott <i>et al.</i> (1999)	Population		DSM-IV	USA	7 032	M	Included in Prescott <i>et al.</i> (1999)

^a Alcoholic addiction, alcoholic psychosis, habitual excessive use of alcohol.

^b Alcoholism.

^c Alcoholic liver disease, alcoholic psychosis, alcohol intoxication, alcoholism.

^d Male and female twin groups were combined in the analysis.

^e Unpublished.

^f Code 303.

Table 2. Adoption studies of alcohol abuse and dependence

Author (year)	Ascertainment	Assessment	Diagnostic measure	Country	N	Relationship	Data
Included							
Cloninger et al. (1981)	Stockholm adoption registry	Temperance board	Registration	Sweden	1724	Biological mother and father with son	Contingency tables
Sigvardsson et al. (1996)	Gothenburg adoption registry	Temperance board	Registration	Sweden	2474	Biological mother and father with son and daughter	Contingency tables
Cadoret et al. (1987)	Iowa children's and family services adoption records	Telephone interview	DSM-III	USA	320	Biological parent with son	Contingency tables
Goodwin et al. (1973)	Copenhagen adoption study	Clinical interview	Blind coding of interviews	Denmark	108	Biological parent with son	Contingency tables
Bohman et al. (1981)	Stockholm adoption registry	Temperance board	Registration	Sweden	1826	Biological father with daughter	Contingency tables
Goodwin et al. (1977)	Copenhagen adoption study	Clinical interview	Blind coding of interviews	Denmark	96	Biological parent with daughter	Contingency tables

in the original articles are typically not the full statistical model that would be required to reconstruct the data for meta-analysis, but the most parsimonious model for the specific study. However, most studies reported the tetrachoric correlations or odds ratios (ORs) and the prevalence rates, which allowed us to reconstruct the raw data with equivalent population parameters. Tests of heterogeneity within the twin models relied upon this recreated data (effectively resulting in a mega-analysis). Among the adoption studies, some presented ORs while others presented the percent affected in the sample. To put everything on the same metric and to make the adoption studies comparable to the twin studies, we generated raw data from contingency tables from the adoption studies and then computed tetrachoric correlations.

In the twin analysis, heritabilities were estimated using standard structural equation modeling techniques that compare the tetrachoric correlations between multiple groups of twins separated by sex and zygosity (Neale & Cardon, 1992). To assess qualitative genetic sex differences a parameter was included that allowed the correlation between the genetic factors of opposite-sex DZ twins to be smaller than the same-sex DZ correlation (Neale & Cardon, 1992). If significant, this would indicate that at least partially different genetic factors culminate in AUD in males and females. Heritability in adoption studies was estimated by comparing the resemblance between biological parents and their adopted-away offspring, modeled as half the additive genetic variance. This allowed us to analyze the adoption and twin studies jointly within the SEM framework.

No measure comparable to shared environment from twin studies was available from the adoption studies, so in comparing twin and adoption studies we focused solely on the estimates of heritability.

Likelihood ratio tests were used to test for the significance of each of the variance components. Importantly, because twin studies focus on variance, which must be a positive quantity, the likelihood ratio tests for significance is not distributed as a χ^2 with, for example, 1 df. Instead, the null distribution is a 50:50 mixture of 0 and χ^2 with 1 df (Wu & Neale, 2012). The presented hypothesis tests take this finding into account.

To test for heterogeneity across samples for the various parameters of interest, we used a likelihood ratio test to compare the full model to the restricted model. Twice the difference between the log-likelihoods of the two models is, under certain regularity conditions, distributed as χ^2 with degrees of freedom equal to the difference in the number of parameters in the two models. Thus, to test for heterogeneity in, e.g. the genetic parameter, we compared the model

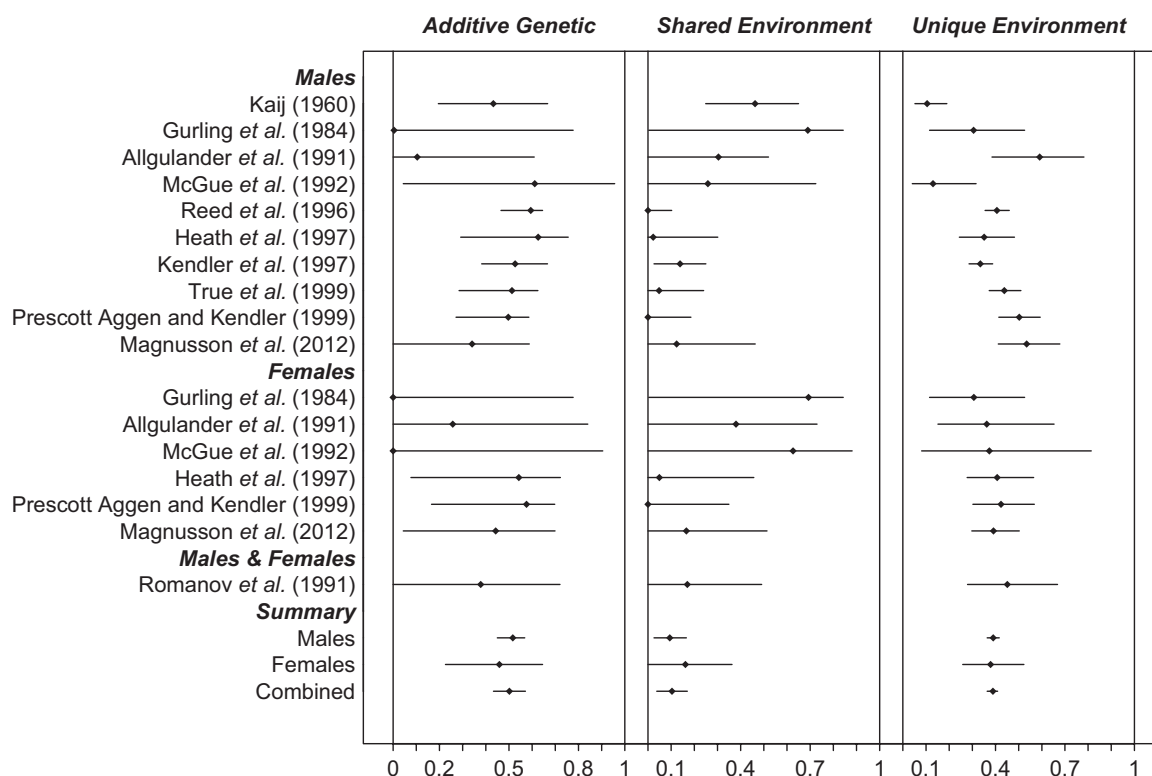


Fig. 1. Forest plot of genetic and environmental variance components for alcohol use disorders in twin studies by sex.

where all of the studies had unique genetic parameters to a model where all of the genetic parameters across the studies were equated. This is a multiple degrees-of-freedom test. To test for heterogeneity across sexes, assessment methods, or study design, we relied on a 1 df likelihood ratio test. For example, to test for genetic heterogeneity across sexes, we compared a model with one genetic parameter for males and one for females, to a restricted model where the genetic parameters were equated across sex. All modeling was performed in OpenMx (Boker *et al.* 2011, 2012).

Results

Twin studies

Additive genetic effects

The combined estimate of the heritability of AUDs in the twin studies was 0.51 [95% confidence interval (CI) 0.45–0.56]. We first examined whether there was heterogeneity in the heritability estimate as a function of sex – that is testing for quantitative sex effects. As can be seen in Fig. 1 and Table 3, the genetic effects on AUD can be equated across samples both within men ($\chi^2=11.63$, $df=11$, $p=0.39$) and women ($\chi^2=4.58$, $df=7$, $p=0.71$), and across both men and women ($\chi^2=0.47$, $df=1$, $p=0.49$) without a reduction in the model fit, consistent with minimal heterogeneity.

When examined separately, the heritability of AUD was estimated at 0.52 in males (95% CI 0.45–0.57) and 0.44 in females (95% CI 0.25–0.61). In addition, we found no evidence for qualitative sex differences in genetic effects for AUDs. Specifically, the ratio of the correlation between opposite-sex and same-sex twin pairs did not differ significantly from unity ($r_{g-mf}=1$, 95% CI 0.42–1.00, $\chi^2=1.79$, $df=4$, $p=0.77$), albeit with very large CIs, which suggests that the same genes contribute to AUD risk in both males and females.

The second contrast tested whether the heritability estimate differed as a function of the assessment method. Specifically, several studies used population registries or hospital records to infer AUD while others relied on clinical interviews. There was no statistically significant difference between the assessment methods ($\chi^2=0.31$, $df=1$, $p=0.58$). Accordingly, there is no evidence of heterogeneity in the heritability estimate due to sex or assessment method. The likelihood ratio tests results are presented in Table 4.

Shared environmental effects

A forest plot of the shared environmental variance components is presented in the middle panels of Fig. 1 and in Table 3. The combined estimate of the shared environmental variance proportion for AUDs across all studies was modest 0.10 (95% CI 0.03–0.16) but

Table 3. Parameter estimates and confidence intervals (CI) for twin studies of alcohol use disorders

Relationship	Study	Heritability		Shared environment		Unique environment	
		Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Male twins	All twins	0.510	0.448–0.556	0.095 ^a	0.033–0.158	0.393	0.375–0.415
	All males	0.516	0.447–0.567	0.083 ^a	0.015–0.149	0.391 ^a	0.367–0.417
	Kaij (1960)	0.402	0.153–0.646	0.481	0.261–0.673	0.118	0.060–0.210
	Gurling et al. (1984)	0.004	0.000–0.777	0.690	0.003–0.843	0.306	0.115–0.526
	Allgulander et al. (1991)	0.161	0.000–0.630	0.263	0.000–0.508	0.576	0.368–0.777
	Caldwell & Gottesman (1991), Romanov et al. (1991)	0.772	0.242–0.937	0.000	0.000–0.456	0.228	0.063–0.560
	McGue et al. (1992)	0.585	0.021–0.950	0.275	0.000–0.734	0.140	0.047–0.328
	Reed et al. (1996)	0.597	0.463–0.648	0.000	0.000–0.107	0.403	0.352–0.458
	Heath et al. (1997)	0.675	0.379–0.779	0.002	0.000–0.246	0.323	0.221–0.450
	Kendler et al. (1997)	0.529	0.384–0.671	0.133	0.019–0.245	0.338	0.289–0.391
	True et al. (1999)	0.510	0.277–0.621	0.044	0.000–0.240	0.446	0.379–0.519
	Prescott et al. (1999)	0.489	0.294–0.578	0.000	0.000–0.156	0.511	0.422–0.609
	Knopik et al. (2004)	0.599	0.288–0.694	0.000	0.000–0.260	0.401	0.306–0.511
	Magnusson et al. (2012)	0.335	0.000–0.573	0.104	0.000–0.431	0.561	0.427–0.714
	Female twins	All females	0.441	0.246–0.605	0.158	0.000–0.327	0.400
Gurling et al. (1984)		0.000	0.000–0.777	0.693	0.003–0.843	0.307	0.115–0.526
Allgulander et al. (1991)		0.229	0.000–0.818	0.383	0.000–0.720	0.388	0.173–0.672
Caldwell & Gottesman (1991)		0.091	0.000–0.876	0.652	0.000–0.868	0.257	0.069–0.523
McGue et al. (1992)		0.000	0.000–0.904	0.626	0.000–0.881	0.374	0.081–0.814
Heath et al. (1997)		0.603	0.112–0.738	0.007	0.000–0.435	0.390	0.262–0.553
Prescott et al. (1999)		0.591	0.189–0.706	0.001	0.000–0.343	0.409	0.294–0.545
Knopik et al. (2004)		0.529	0.130–0.649	0.015	0.000–0.357	0.456	0.351–0.578
Magnusson et al. (2012)		0.404	0.024–0.705	0.205	0.000–0.523	0.390	0.289–0.511
Male and female twins		Romanov et al. (1991)	0.385	0.000–0.721	0.165	0.000–0.491	0.449

^a Parameter has significant heterogeneity.

Table 4. Model comparison results for twin studies

Name	Number of estimated parameters	–2LL	AIC	χ^2	df	<i>p</i>
Full model	89	68 205.34	–238 084.7	–	–	–
Equal A – males	78	68 216.96	–238 095.0	11.626773	11	0.39
Equal C – males	78	68 227.78	–238 084.2	22.444837	11	0.02
Equal E – males	78	68 260.04	–238 052.0	54.699729	11	0.00
Equal A – females	82	68 209.92	–238 094.1	4.585781	7	0.71
Equal C – females	82	68 213.57	–238 090.4	8.237681	7	0.31
Equal E – females	82	68 208.44	–238 095.6	3.107698	7	0.87
Equal r_{g-mf}	85	68 207.13	–238 090.9	1.791517	4	0.77
Equal A – all	70	68 220.26	–238 107.7	14.923547	19	0.73
Equal C – all	69	68 236.65	–238 093.3	31.314067	20	0.05
Equal E – all	70	68 263.25	–238 064.7	57.914781	19	0.00

AIC, Akaike's Information Criterion.

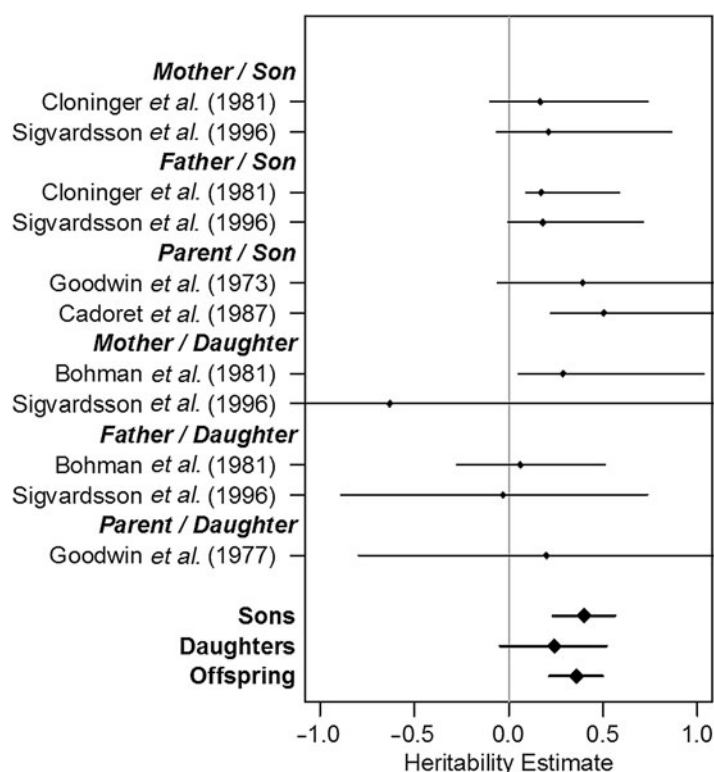


Fig. 2. Forest plot of heritability of alcohol use disorders from adoption studies by relationship.

statistically significant ($p < 0.01$). Heterogeneity in the common environmental variance component was also tested as a function of both sex and assessment technique. Across all studies, the estimate of shared environmental effects on AUDs in males was modest (0.083, 95% CI 0.01–0.15) and statistically heterogeneous ($\chi^2 = 22.44$, $df = 11$, $p = 0.02$). As is evident in the figure, this heterogeneity derived largely from a single study: Kaij (1960). When this study was removed, the heterogeneity decreased substantially and became non-significant ($\chi^2 = 9.97$, $df = 10$, $p = 0.44$). However, when this study was excluded from our analysis, the shared environment effect in males was no longer statistically significant (0.05, 95% CI 0.00–0.12, $\chi^2 = 1.92$, $df = 1$, $p = 0.17$). In females, the estimate of shared environmental effects was relatively large and marginally statistically significant ($\chi^2 = 0.16$, 95% CI 0.00–0.33, $\chi^2 = 3.06$, $df = 1$, $p = 0.08$), and there was no heterogeneity across samples ($\chi^2 = 8.24$, $df = 7$, $p = 0.31$). When the common environmental parameters were equated across sex, excluding the Kaij outlier, there were no significant differences between the sexes ($\chi^2 = 1.46$, $df = 1$, $p = 0.22$).

Consistent with the heritability estimates, the comparison of estimates of shared environmental effects in studies using hospital discharge or registration records *v.* clinical interviews was not statistically significant ($\chi^2 = 0.27$, $df = 1$, $p = 0.60$). The heterogeneity contrast was unaffected by the inclusion or exclusion of the Kaij study.

Unique environmental effects

The combined estimate of the unique environment proportion of variance is 0.39 (95% CI 0.38–0.42). There was strong heterogeneity in the estimates of the non-shared environment in males ($\chi^2 = 54.70$, $df = 11$, $p < 0.001$). Given that the Kaij sample had the smallest non-shared parameter estimate, the heterogeneity analysis was re-run with a fixed effect for the Kaij study parameter. While the heterogeneity in the unique environmental parameter was considerably reduced, it was still significant ($\chi^2 = 31.30$, $df = 10$, $p < 0.001$) and therefore not a function of a single study. In contrast, in females there was no evidence of heterogeneity ($\chi^2 = 3.11$, $df = 7$, $p = 0.87$). While there was heterogeneity within the male unique environmental estimate, when the estimates of the unique environmental parameter across sexes was constrained to equality, there were no significant differences between the sexes ($\chi^2 = 0.04$, $df = 1$, $p = 0.83$). Thus, there are no significant differences in estimates of the unique environmental variance for males and females.

When comparing the unique environmental estimate as a function of assessment method, excluding the Kaij outlier study, there was no significant heterogeneity in the parameter estimates ($\chi^2 = 0.27$, $df = 1$, $p = 0.60$). Follow-up tests were conducted to test for heterogeneity within each assessment group. Significant

Table 5. Model comparison results for adoption studies

Parameters equated	Estimated parameters	–2LL	AIC	χ^2	df	<i>p</i>
Full model	33	8 114.85	–17 371.2			
Sons equated	28	8118.46	–17 377.5	3.61	5	0.61
Daughters equated	29	8 117.73	–17 376.3	2.88	4	0.58
All offspring equated	23	8 122.26	–17 383.7	7.42	10	0.69

AIC, Akaike's Information Criterion.

Table 6. Parameter estimates and 95% confidence intervals (CI) for adoption studies^a

Relationship	Study	Heritability estimate	95% (CI)
Summary	All offspring	0.356	0.216 to 0.499
	Male offspring	0.400	0.235 to 0.562
	Female offspring	0.241	–0.045 to 0.517
Mother/son	Cloninger <i>et al.</i> (1981)	0.166	–0.100 to 0.738
	Sigvardsson <i>et al.</i> (1996)	0.210	–0.062 to 0.865
Father/son	Cloninger <i>et al.</i> (1981)	0.172	0.092 to 0.588
	Sigvardsson <i>et al.</i> (1996)	0.181	–0.005 to 0.711
Parent/son	Cadoret <i>et al.</i> (1987)	0.504	0.222 to 1.555
	Goodwin <i>et al.</i> (1973)	0.392	–0.061 to 1.426
Mother/daughter	Bohman <i>et al.</i> (1981)	0.287	0.053 to 1.034
	Sigvardsson <i>et al.</i> (1996)	–0.630	–1.800 to 1.249
Father/daughter	Bohman <i>et al.</i> (1981)	0.062	–0.276 to 0.513
	Sigvardsson <i>et al.</i> (1996)	–0.031	–0.889 to 0.736
Parent/daughter	Goodwin <i>et al.</i> (1977)	0.200	–0.796 to 1.388

^a The heritability estimate for the adoption studies was estimated by doubling the correlation between the biological parents and offspring (in the same way that the genetic correlation between dizygotic twins is half the genetic correlation of monozygotic twins). Accordingly, the theoretical limits of the confidence intervals is –2 and 2 rather than –1 and 1.

heterogeneity was found for studies using interview-based assessments ($\chi^2=24.68$, $df=14$, $p=0.04$), but not for record-based assessments ($\chi^2=7.08$, $df=4$, $p=0.13$). Taken in concert with the previous findings, the heterogeneity within the interview-based assessment method is primarily a function of heterogeneity in the male unique environmental parameters.

Adoption studies

A forest plot of the heritability estimates for the adoption studies is presented in Fig. 2. Very few of the adoption studies individually produced significant estimates of the heritability of AUDs. However, when analyzed together, the estimate of heritability in males was 40.0% and statistically significant (95% CI 0.23–0.56, $\chi^2=22.15$, $df=1$, $p<0.001$). In females, the estimated heritability of AUDs was modest (0.241) but not statistically significant (95% CI 0.00–0.52, $\chi^2=2.75$, $df=1$, $p=0.05$). When the sexes were combined, no significant differences were seen between them, and the heritability was estimated at 0.36 with

relatively wide CIs (0.22–0.50). The model fitting results for the adoption studies are presented in Table 5 and the parameter estimates are presented in Table 6.

Combined twin and adoption study analyses

Our final analyses tested for heterogeneity across twin and adoption studies. Specifically, two models were estimated that simultaneously evaluated the twin and adoption data. In the first model, two heritability coefficients were estimated: one each for twin and adoption studies. As indicated above, these parameters can be equated across sexes in both types of study. In the second model, we constrained these parameters to equality. When the two models are compared using a likelihood ratio test, the heterogeneity in the heritability estimates of the twin and adoption studies was not statistically significant ($\chi^2=3.51$, $df=1$, $p=0.06$). The overall best estimate of the heritability of AUDs, derived from both twin and adoption studies, was 0.49 with relatively tight CIs (0.43–0.53).

Discussion

The goal of this study was to perform a quantitative meta-analysis of twin and adoption studies of AUD with a specific focus on five questions, which we now review in turn.

First, our best estimate for the heritability of AUDs, based on 13 twin and five adoption studies was 0.49 (95% CI 0.47–0.54). Importantly, while the diagnosis of AUD used in the various studies included in this meta-analysis may have substantial levels of clinical and etiological heterogeneity, the fact that we do not find statistical evidence of differential genetic or environmental heterogeneity as a function of ascertainment or diagnosis implies that the underlying construct of AUD is fairly robust to the specific measure of AUD that is used in any given study. Furthermore, the heterogeneity between AUD in twin and adoption studies was not statistically significant at conventional levels of significance ($p=0.06$). While heterogeneity in the parameter estimate is trending towards significance, given that over 1 00 000 observations were included in the analysis, there is ample power to detect even relatively small differences across samples. Further, we found no evidence for genetic qualitative sex effects for AUD. That is, this result predicts that the same genetic factors increase risk for AUDs in males and females. As such, we find no evidence for any type of genetic sex limitation.

It is of interest to compare these findings with those of two other disorders where twin studies have been subject to similar meta-analyses. In major depression, six twin studies were examined and produced an aggregate heritability estimate of 0.37 (95% CI 0.31–0.42) (Sullivan *et al.* 2000). In schizophrenia, 12 twin studies were available and the meta-analytic heritability estimate was 0.81 (95% CI 0.73–0.90) (Sullivan *et al.* 2003). The estimated heritability of AUDs was in between that found for major depression and schizophrenia, and outside the 95% CIs of both disorders. These results imply that the heritability of psychiatric disorders do genuinely differ from one another (Kendler, 2001).

Second, several early twin and adoption studies suggested that genetic factors were more important in the etiology of AUDs in men than women (Goodwin *et al.* 1973; Bohman *et al.* 1981; McGue *et al.* 1992) while more recent studies sometimes reached different conclusions (Heath *et al.* 1997; Prescott *et al.* 1999). Our results provide strong evidence that despite large and consistent differences in the prevalence of AUDs in the two sexes (Kessler *et al.* 1994; Hasin *et al.* 2007), genetic influences on AUD are similar in magnitude in men and women. The primary reason early twin and adoption studies were unable to detect genetic

factors in AUD in females was due to very small sample sizes and relatively low prevalence rates in the female samples. When we aggregated the data across studies, the estimated heritability of AUDs was indistinguishable in the two sexes.

Third, prior studies have produced contradictory evidence about the presence of shared environmental effects for AUDs. This is partly a problem of statistical power as in the presence of substantial heritable influences, quite large twin samples are needed to detect reliably modest shared environmental effects (Neale *et al.* 1994). Our meta-analysis suggests the presence of modest, though statistically significant, shared environmental influence on risk for AUDs. Our twin findings predict that the correlation in liability for AUDs in siblings should be equal to $0.49/2 + 0.10 = 0.35$ of which approximately one third comes from shared environmental and two-thirds from genetic sources of resemblance.

Fourth, the twin studies that we examined used two quite different methods of ascertainment and assessment. One set of studies assessed AUDs via personal interviews, which require subjects to both cooperate and accurately report their AUD symptoms. Another set of studies used registry information, which may be less sensitive but eliminates problems of cooperation and selective recall. Thus, there is considerable heterogeneity in the diagnostic assessments of AUD. In neither the genetic nor the common environmental variance components did the method of assessment induce heterogeneity in the parameter estimates. Accordingly, we can conclude that the method of assessment does not significantly affect estimates of the genetic or common environmental variance components.

Finally, human researchers are provided with two major ‘experiments of nature’ to disentangle genetic and environmental effects: twin and adoption studies. Only rarely are the results of these two methods – which have different strengths and potential limitations – quantitatively compared. For example, in a meta-analytic analysis of the genetics of antisocial behavior, Rhee and Waldman find that heritability estimates are lower in adoption than in twin studies (Rhee & Waldman, 2002). We are fortunate in the field of AUD to have a reasonable number both of high quality twin and high quality adoption studies. Our results show that while heritability estimates are modestly lower for AUD when derived from adoption than from twin studies, the estimates are statistically homogeneous. That is, within the power of the available studies, we obtain the same estimate of the heritability of AUDs from these two main genetic epidemiologic methods. Given the differences in their approach and their distinct potential methodological limitations, we

should be considerably more confident in our conclusions about the heritability of AUD given that we obtain similar results from both methods than we could having results from only one of them.

Limitations

These results should be interpreted in light of four potential methodological limitations. First, obtaining parameter estimates from clinically ascertained twin studies required an estimated population prevalence of AUD. We utilized the prevalences contained in each report. If these were inaccurate some bias might have been introduced into the current estimates.

Second, estimates of shared environmental effects can be biased upward by assortative mating for AUDs. This is because when spouses have correlated liabilities for AUD, the correlation between the genetic factors of DZ twins and siblings would be higher than 0.5, which is assumed in the model. The spousal correlation for AUD was estimated at equal to +0.12 as found in one prior large-scale general population study (Maes *et al.* 1998). If this spousal resemblance results entirely from assortative mating (spouses choosing one another, directly or indirectly, on the basis of their genetic risk for AUD) rather than spousal interaction (spouses mutually influencing each other's drinking and hence liability to AUD), then inflation of the shared environmental variance component would be ~0.06, a little over half of the estimated shared environmental variance component from the meta-analysis. Accordingly, some proportion of our estimate of shared environmental effects for AUD may be a result of assortative mating.

Third, estimates of latent genetic factors in the Classical Twin Design (CTD) formally assume additive genetic effects. The meager proportions of variance that are accounted for by individual genetic variants have led some to conclude that gene-environment interactions or non-additive genetic factors (such as epistasis or dominance) may play pivotal roles in the etiology of AUD. With the CTD it is generally not possible to disentangle the effects of non-additive genetic factors from additive genetic factors (Martin *et al.* 1978; Neale *et al.* 1994) due to the lack of power to disentangle these highly collinear genetic factors. Furthermore, when the DZ correlation is greater than half the MZ correlation, most researchers do not even test for dominance as the correlations are more consistent with the shared environment playing a role in the development of the phenotype. More recent evidence, however, suggests that non-additive genetic variation is absorbed into the additive genetic factor (Keller *et al.* 2010), suggesting that the genetic variance component should be interpreted as a broad genetic factor.

This interpretation is consistent with our interpretation of the current results.

Fourth, the possible effects of year of birth and age at assessment were not accounted for in this study. Secular trends in the use and availability of alcohol may have contributed to or obscured sample heterogeneity. The one outlier study by Kaij was also the first, and its unusual estimates may have been partly due to unusual population prevalence or other characteristics of that sample.

Conclusions

There is substantial consistency in the estimates of genetic and shared environmental variance in liability to AUD. In particular, we found no significant differences between the estimates derived from twin studies and adoption studies, from studies relying on personal interviews *v.* official records for the assessment of AUD or from studies of males *v.* females. Furthermore by including a large number of studies into the analysis, we were able to detect significant shared environmental effects that account for ~10% of the variance in AUD. These findings should enhance our confidence in the validity of our heritability estimates for AUD and provide a firm footing for efforts now well underway to try to localize on the human genome the specific genetic variants that contribute to the genetic risk for AUD.

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Declaration of Interest

None.

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