0145-6008/91/1501-0122$3.00/0
ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

Vol. 15, No. 1
January/February 1991

Intoxication after an Acute Dose of Alcohol: An Assessment of Its Association with Alcohol Consumption Patterns By using Twin Data

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We examined the hypothesis that genetically determined differences in sensitivity to alcohol explain some of the genetic variation in alcohol consumption pattern. Self-report data on average weekly alcohol consumption and self-ratings of intoxication after a standard dose of ethanol (0.75 g/kg body weight), used as an index of sensitivity, were obtained on 206 Australian twin pairs. Significant genetic covariance between weekly consumption and level of intoxication after alcohol intake was found in males, lower ratings of intoxication being associated with increased consumption. However, when direction of causation models were fitted to the male twin data, the hypothesis that decreased sensitivity was a cause of increased consumption was rejected. The major causal effect was that of weekly consumption on level of sensitivity. A similar, although nonsignificant, trend was observed in females. The strength of the association between self-report of average weekly consumption and level of intoxication after a standard dose of alcohol supports the validity of the former measure.

Key Words: Alcohol Consumption, Alcohol Challenge, Twins.

DESPITE shortcomings of individual studies,[1] findings from studies of adoptees,[2–4] of half-siblings,[5] and of twins[6–9] are broadly consistent in indicating a significant genetic contribution to vulnerability to alcoholism in males. Negative findings using the twin design[10,11] probably result from small sample size, particularly because the strong assortative mating that occurs for alcoholism[12] greatly reduces the power of the twin study.[13,14] Surveys of drinking practices in general community samples of twins have also demonstrated a strong genetic influence on alcohol consumption patterns in nonalcoholics of both sexes.[8,15–23]

Given this important genetic contribution to the natural history[24] of alcohol use and abuse, an understanding of the mechanisms by which such genetic influences act is desirable. Selective breeding experiments in rodents[25,26] have demonstrated a genetic influence on "ethanol consumption, initial central nervous system sensitivity, ability to acquire tolerance, and expression of withdrawal symptoms."[27] A laboratory-based twin study has demonstrated a genetic contribution to sensitivity to alcohol, as assessed by increase in body sway, deterioration in psychomotor performance, and differences in subjective ratings of intoxication, in response to an acute dose of alcohol.[28–30] High-risk studies of the sons of alcoholics and controls have demonstrated a decreased reactivity to alcohol in the former group which, it is hypothesized, may mediate the genetic influence on alcholism.[31] Sons of alcoholics report less intoxication[32–35] and exhibit a smaller increase in body sway,[36] diminished cortisol response,[37,38] and more rapid recovery of normal prolactin levels[39,40] after a standard dose of alcohol.

An inevitable disadvantage of high-risk studies is their reliance on subjects who are not alcohol-naive. Despite attempts to match sons of alcoholics and controls for current consumption patterns,[31] differences in drinking history might explain apparent differences in sensitivity to alcohol. The conventional twin design can provide important information in this regard. Even in cross-sectional twin data, provided that two correlated traits have somewhat different inheritance patterns, so that either monozygotic or dizygotic twin correlations (or both) differ for the two traits, and provided that adequately large sample sizes are available,[41] it is possible to resolve alternative hypotheses about direction of causation.[42] In this paper, therefore, we reanalyze data of Martin et al.[43] on habitual alcohol consumption patterns and self-report intoxication in responses to an acute dose of alcohol, using direction of causation models, to determine to what degree differences in alcohol consumption pattern are a consequence of differences in sensitivity to alcohol and to what extent they are a cause of such sensitivity differences.

METHODS

Sample and Protocol

Subjects were 206 twin pairs (43 MZ female, 42 MZ male, 44 DZ female, 38 DZ male, and 39 unlike-sex DZ pairs), aged 18–34 yr, recruited through the Australian NH&MRC Twin Registry, who were alcohol free at the beginning of testing and who successfully completed the experimental protocol.[28,43] Zygosity was determined by blood typing.[43] Members of a twin pair were tested on the same day, beginning at about 9:00 AM, having been instructed to eat a light, nonfatty breakfast ~1 hr earlier. Twins completed a questionnaire about their habitual

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Received for publication March 12, 1990; accepted August 28, 1990.

This research was supported by Alcohol, Drug Abuse, and Mental Health Administration Grants AA07728, AA07535, MH40828, and DA05588, and by a grant from the Australian Associated Brewers.

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alcohol consumption patterns, including average weekly consumption, over the preceding 12 months, of beer, wine, spirits, sherry, and other alcohol beverages. From this, each subject's average weekly consumption in standard drinks of alcohol (x) was computed, and log (x + 1) transformed. After baseline assessments of subjective intoxication, body sway, and other measures of psychomotor performance, each twin was given an alcohol dose of 0.75 g ethanol/kg body weight, diluted to 10% in sugarless squash, which was consumed under supervision over a 20-min period at a constant rate. After a further 20 min, the first of three hourly cycles of testing began, measurements of breath alcohol, blood alcohol, psychomotor performance, body sway, and self-ratings of intoxication being obtained.[43] We consider only the results from the first testing cycle. To assess subjective intoxication, subjects, asked "How drunk do you feel now?", were asked to provide ratings on a 10-point scale, with 1 = "quite sober" and 10 = "the most drunk I have ever been."[39,43] Any twins who had positive blood alcohol levels at baseline assessment was excluded from the study, and so all subjects remaining in the study reported (correctly) that they were quite sober at the baseline assessment. Two to six twin pairs were tested on each day, and co-twins were never tested consecutively, to minimize the possibility of observer bias.

The exact phrasing of the intoxication question requires some consideration, because it encourages respondents to give relative ratings of their level of intoxication, compared with the occasion when they have been most intoxicated. Those whose maximum consumption ever was very high would be expected to give low intoxication ratings compared with those with a lower maximum consumption. Our measure of sensitivity to alcohol, therefore, is probably assessing the maximum amount of alcohol that an individual has been able to consume on a single occasion, relative to the standard dose given in the experimental protocol. In addition to questions about average weekly consumption, we also asked subjects whether they had ever been drunk and whether they had ever had a hangover. Regrettably, we have been unable to recover the data for these items, which might have been even stronger predictors of intoxication ratings than average consumption.

Genetic Analysis

Covariance matrices were computed separately for each zygosity group, giving the variances and covariances of first twin's and second twin's average weekly alcohol consumption and post-alcohol intoxication rating. Although the intoxication rating was a polychotomous variable, we decided to analyze it as though it were continuous. We considered an alternative approach, that of estimating polychoric and polyserial correlations for this variable. However, because of the relatively large number of response categories and small sample sizes for each twin group, some expected cell frequencies in the two-way contingency table for intoxication rating would be very low, giving rise to potentially serious biases in the estimates of the polychoric coefficient.[44] For data summary, twins from a pair were assigned as first or second twins at random, in the case of like-sex twin pairs, but the female twin from unlike-sex pairs was always designated the first twin. Bivariate genetic and environmental models were fitted to the covariance matrices by the method of maximum likelihood using LISREL.[42,45,46] This yielded a χ^2 goodness of fit statistic and a significant χ^2 indicating failure of the model to account for the observed data. The goodness of fit of a general model, and a nested submodel, were compared by likelihood ratio χ^2,[45,47] a statistic which is computed as the difference in goodness of fit χ^2 between the submodel and a more general model. A significant likelihood ratio χ^2 indicates that the submodel gives a significantly worse fit than the more general model.

Fig. 1 presents a bivariate path model[48] that represents the contribution of genetic and environmental effects to the variance and covariance of two traits measured in twin pairs. The full model allows for additive genetic effects (which will reflect the additive effects of multiple genetic loci), nonadditive genetic effects (arising through genetic dominance or through epistatic interactions between loci), shared environmental effects (which are assumed to be no more highly correlated in monozygotic than in dizygotic twin pairs), and nonshared environmental effects (i.e., those differences in environmental experience that make one twin differ from his or her cotwin). Nonadditive genetic effects and shared environmental effects are confounded in twin data, the former tending to produce a dizygotic twin correlation that is less than one-half the monozygotic twin correlation, and the latter to produce a dizygotic correlation that is greater than one-half the monozygotic correlation.[13,49,50] As represented in Fig. 1, the model allows for common factor genetic and environmental effects that influence both consumption and intoxication, and specific factor genetic and environmental effects that only influence (i.e., are specific to) consumption. An alternative model would allow for common factor effects, and effects specific to intoxication instead of consumption. In general, the two parameterizations of this model will give an identical fit to the data unless, in addition to additive genetic and nonshared environmental effects, there are major nonadditive genetic influences on one trait, and shared environmental influences on the second trait. With only two variables, we cannot estimate simultaneously common factor effects and effects specific to each variable.[42]

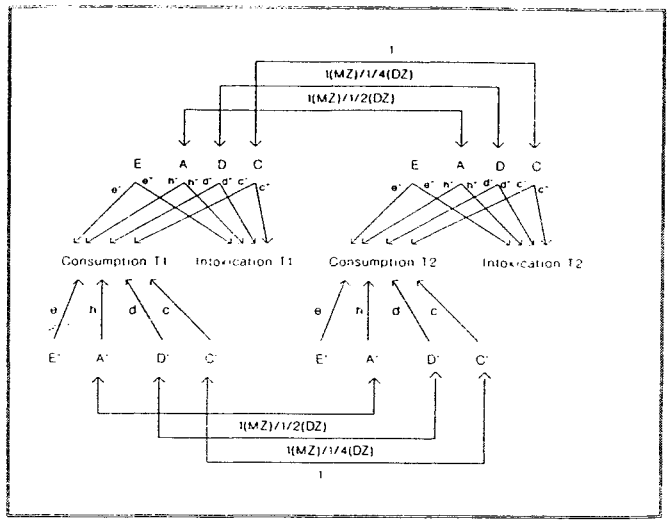

Fig. 1. General bivariate model for causes of twin resemblance. E, A, D, and C denote nonshared environmental, additive genetic, dominance genetic, and shared environmental influences common to both consumption and intoxication; E', A', D', and C' denote corresponding effects specific to consumption. Paths from the latent variables to consumption, or intoxication, are denoted by lower case letters. Two-headed arrows are used to denote correlations between latent variables.

Bivariate genetic and environmental models were fitted separately to the data on male like-sex pairs, on female like-sex pairs, and on all five zygosity groups. All models allowed for nonshared environmental effects, because the responses of monozygotic twin pairs were not perfectly correlated for either trait. We compared the fit of four basic models for twin resemblance: (1) an environmental model, allowing for shared environmental effects only (h=h'=h''=d=d'=d''=0); (2) an additive genetic model (c=c'=c''=d=d'=d''=0); (3) an additive genetic plus shared environmental model (d=d'=d''=0); and (4) an additive plus non-additive genetic model (c=c'=c''=0). In the joint analysis of all five zygosity groups, we fitted both sex-independent models, under which the values of genetic and environmental parameters were the same in males and females; and sex-dependent models, which allowed for sex-differences in genetic and environmental parameters. Because of the relatively small sample sizes,[13] major effects of genotype x sex interaction could remain undetected in these data, and give rise to a serious bias in the parameter estimates under the sex-independent model. If the unlike-sex dizygotic twin correlations were lower than the corresponding like-sex correlations, for example, this would tend to inflate our estimate of nonadditive genetic effects under the sex-independent model.

Direction of Causation Models

We also tested three submodels of the general bivariate models: (1) differences in habitual alcohol consumption are a cause of differences in

ratings of intoxication; (2) differences in sensitivity to alcohol (assessed by ratings of intoxication) are a cause of differences in alcohol consumption pattern; (3) there is reciprocal interaction between alcohol sensitivity and habitual alcohol consumption, such that decreased sensitivity leads to increased consumption, and increased consumption further decreases sensitivity to alcohol. Model 3, of which models 1 and 2 are special cases (setting i'=0 or i=0, respectively) is represented diagramatically in Fig. 2. These submodels assume that the only causes of the correlation between habitual alcohol consumption and intoxication ratings after alcohol are the causal effect of consumption on sensitivity and the causal effect of sensivity on consumption. If both sensitivity and consumption are being influenced by a third variable, then we would expect these three submodels to give a poor fit to the data, compared with the fit of the general bivariate models.[42]

In fitting these submodels, we allowed for additive genetic effects plus either nonadditive genetic effects or shared environmental effects on each trait. Omission of effects from the model that were nonsignificant because of the small sample sizes might nonetheless bias the estimates of the direction of causation parameters. To avoid bias arising from undetected genotype x sex interaction, we fitted models only to like-sex pairs.

To understand the informativeness of cross-sectional twin data for testing hypotheses about direction of causation, it is helpful to consider a simplified version of the model in Fig. 2, where h'=0. This implies that, except for the genetic influence that is mediated through consumption (if i≠0), twin pair resemblance for sensitivity is entirely the result of shared environmental influences; and, except for the influence of shared environment that is mediated through sensitivity (if i≠0), twin pair resemblance for consumption is entirely the result of genetic influences. If we consider the further simplified cases where (i) the only causal influence is that of consumption on sensitivity (i'=0) or (ii) the only causal influence is that of sensitivity on consumption (i=0), then we find that these two alternatives lead to different predictions for the cross-correlation between the two traits, i.e., between first twin's sensitivity, and the cotwin's consumption, and vice versa. In case i, the cross-correlation will be determined by twin pair resemblance for consumption (which is genetic in origin) and by the causal influence of consumption on sensitivity (i), so that the corss-correlations will be predicted to be higher for monozygotic than for dizygotic pairs. In case ii, the cross-correlation will be determined by twin pair resemblance for sensitivity (which is determined by shared environmental factors) and by the causal influence of sensitivity on consumption (i'), so that the cross-correlation is expected to be the same for monozygotic as for dizygotic pairs. The same reasoning will apply more generally, even if the two traits are influenced by both genetic and shared environmental effects, provided that the relative importance of these sources of variation differs between traits.

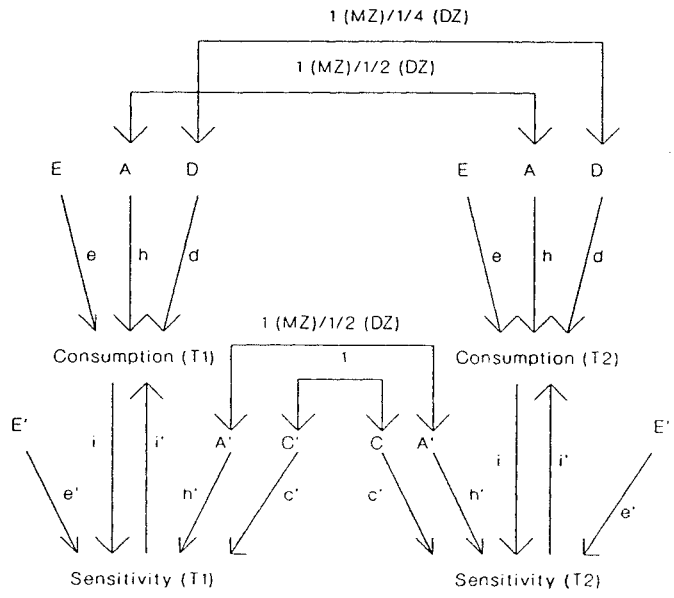

Fig. 2. Reciprocal interaction model for consumption and sensitivity. E, A, and D denote nonshared environmental, additive genetic, and dominance genetic effects on consumption; E', A', and C' denote corresponding nonshared environmental, additive genetic, and shared environmental effects on sensitivity. Path i represents the causal influence of consumption on sensitivity, i' that of sensitivity of consumption.

RESULTS

All subjects had previously used alcohol, although 12.3% of female twins and 9.6% of male twins reported that they did not consume any alcoholic beverages in a typical week. Average daily consumption figures were 10.01 g absolute alcohol/day for females, and 19.28 g/day for males. Some 3.3% of females and 15.2% of males reported using an average of >40 g absolute alcohol/day. The female statistics were very close to the average found for female drinkers in a survey of drinking and smoking habits conducted in 1977 by the Australian Bureau of Statistics[51] (9.36 g for female drinkers aged 18–24, 10.04 g for female drinkers aged 25–44). The male figures are somewhat lower than the average for male drinkers[51] (28.5 g for male drinkers aged 18–24, 28.95 g for male drinkers aged 25–44). A mailed questionnaire survey of twins on the Australian NH&MRC Twin Register conducted in 1981[21,52] likewise found a lower value for average consumption by young male drinkers (21.23 g for the 18–24 age group, 23.81 g for the 25–44 group) than had been expected on the basis of the ABS statistics, but rather comparable figures for young female drinkers (8.13 g for 18–24 yr-old, 8.29 g for 25–44 year olds). The lower male consumption figures were attributed to undersampling of very heavy male drinkers and a possible secular trend in drinking practices,[52] two factors which may also apply to the males in the alcohol challenge sample.

Fig. 3 gives the frequency distribution of intoxication ratings for each sex. Only a small minority of males (12.1%), but a somewhat higher proportion of females (20.7%), gave the highest rating indicating they were the most drunk they had ever been. Five males gave the lowest

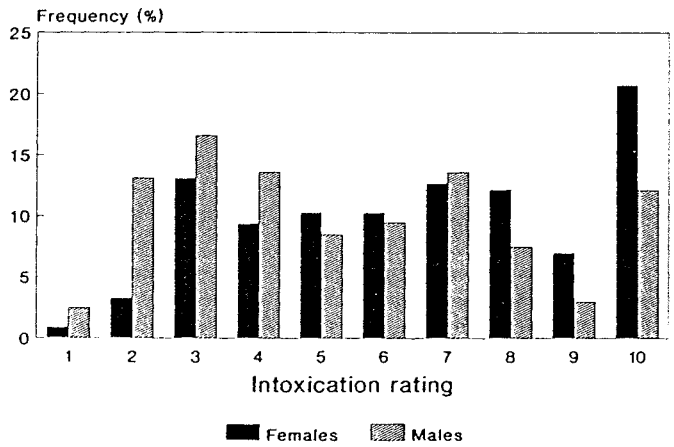

Fig. 3. Frequency distribution of ratings of intoxication as a function of sex.

rating, claiming that they were quite sober. Most subjects gave intermediate ratings.

Table 1 gives the covariance matrices for each twin group, with correlations given in the upper triangle of each matrix. There is a strong negative association between weekly alcohol consumption and intoxication rating, within-person correlations ranging from −0.113 (in female twins from unlike-sex pairs) to −0.649 (in male second twins from monozygotic pairs). Monozygotic twin correlations for each variable (0.560 for consumption and 0.478 for intoxication in female MZ pairs, and 0.706 and 0.483 in male MZ pairs) were higher than the corresponding like-sex dizygotic correlations (0.351 and −0.023; 0.244 and 0.146, respectively), consistent with a genetic influence on both alcohol consumption and intoxication rating. The cross-correlations between alcohol consumption in one twin and the intoxication rating of the cotwin, and vice versa, were likewise higher in absolute value in monozygotic than in dizygotic pairs (−0.513, −0.249, in female MZ pairs, compared with 0.062, −0.071 in female DZ pairs; and −0.610, −0.543 in male MZ pairs, compared with −0.254, −0.053 in male DZ pairs), implying a genetic contribution to the correlation between these two variables.

Results under Bivariate Genetic Model

Table 2 summarizes the results of fitting bivariate genetic models. In the male like-sex analysis and in the analyses of the full sample with or without sex-dependent effects, the shared environmental model gave a significantly worse fit by likelihood ratio χ^2, than the additive genetic plus shared environmental model (χ^2_3=9.81, p=0.02; χ^2_6=16.94, p=0.009; χ^2_3=16.33, p<0.001), whereas the additive genetic model did not (χ^2_3=0.03, p=0.99; χ^2_6=0.70, p=0.99; χ^2_6=0.00, p=1). Adding a nonadditive genetic parameter did not give a significant improvement in fit over the additive genetic model (χ^2_3=0.47, p>0.05; χ^2_6=1.92, p>0.05; χ^2_6=1.40, p>0.05). In the female like-sex analysis, however, neither the additive genetic nor the shared environmental models gave significantly worse fits than the additive genetic plus shared environmental models, so the causes of female twin pair resemblance could not be resolved.

Table 3 summarizes estimates of the proportions of variance in consumption and in intoxication accounted for by common and specific genetic and environmental effects. These were calculated from the maximum likelihood estimates of the parameters h′, h″, h etc. of Fig. 1. For example, the common factor genetic variance component for consumption is computed as h'^2/V', and the specific factor genetic variance as h^2/V', where $V' = h'^2+h^2+c'^2+c^2+e'^2+e^2$ is the total variance in consumption predicted at the maximum likelihood solution. In the case of male like-sex pairs, the results obtained under the additive genetic model are given. For female like-sex pairs, results under the additive genetic plus shared environmental model are given, because neither the additive genetic model nor the shared environmental model could be rejected. We have also calculated the contributions to the within-person correlation between weekly consumption and intoxication rating of common factor genetic effects ($h'h''/V'$ is 0.52 in males and 0.29 in females), where $V=(V'V'')^{0.5}$ and $V'' = h''^2+c''^2+e''^2$ is the predicted variance in sensitivity; common factor shared environmental effects ($c'c''/V'$ is 0 in males and 0.02 in females) and common factor nonshared environmental effects ($e'e''/V'$ is 0.05 in males and 0.08 in females). Under these general bivariate models, the association between weekly alcohol consumption and self-report intoxication thus appears to be largely genetic in origin, especially in males.

Table 1. Twin covariance matrices for average weekly alcohol consumption and intoxication after a standard dose of alcohol

	I*	II	III	IV	I	II	III	IV
	Monozygotic female pairs (n = 43 pairs)				Dizygotic female pairs (n = 42 pairs)			
I	0.839	*−0.539*	*0.560*	*−0.249*	0.709	*−0.349*	*0.351*	*−0.071*
II	−1.269	6.597	*−0.513*	*0.478*	−0.650	4.888	*0.062*	*−0.023*
III	0.450	−1.157	0.772	*−0.407*	0.302	0.139	1.044	*−0.181*
IV	−0.650	3.499	−1.020	8.135	−0.166	−0.139	−0.514	7.686
	Monozygotic male pairs (n = 42 pairs)				Dizygotic male pairs (n = 36 pairs)			
I	1.296	*−0.653*	*0.706*	*−0.543*	1.300	*−0.527*	*0.244*	*−0.053*
II	−1.958	6.938	*−0.610*	*0.483*	−1.672	7.751	*−0.254*	*0.146*
III	0.842	−1.684	1.098	*−0.649*	0.315	−0.800	1.275	*−0.403*
IV	−1.806	3.719	−1.989	8.548	−0.149	1.001	−1.123	6.084
					Unlike-sex pairs (n = 39)			
Female twin I					0.842	*−0.113*	*0.250*	*−0.107*
II					−0.236	5.220	*−0.077*	*0.078*
Male twin III					0.248	−0.190	1.174	*−0.392*
IV					−0.248	0.450	−1.068	6.309

Correlations are given as the upper triangle of each matrix (in italics).

* I, twin 1/female twin weekly alcohol consumption; II, twin 1/female twin intoxication rating; III, twin 2/male twin weekly alcohol consumption; IV, twin 2/male twin intoxication rating.

Table 2. Comparison of Goodness of Fit of Bivariate Genetic and Environmental Models

	Male like-sex pairs			Female like-sex pairs			Full sample					
							Sex-dependent			Sex-independent		
	df	x^2	p	df	x^2	p	df	x^2	p	df	x^2	p
Shared environment	14	17.49	0.23	14	21.04	0.10	38	44.34	0.22	44	55.16	0.12
Additive genetic	14	7.71	0.90	14	16.55	0.28	38	28.10	0.88	46	38.73	0.70
Additive genetic + shared environment	11	7.68	0.74	11	16.02	0.14	32	27.40	0.70	41	38.73	0.52
Additive + nonadditive genetic	11	7.24*	0.78	11	15.28†	0.17	32	26.18	0.76	41	37.33	0.64

* Model that allows for additive + nonadditive genetic common factor influences plus additive genetic + shared environmental influences specific to intoxication gives a slightly better fit ($x^2_{11} = 7.21, p = 0.78$).

† Model that allows for additive + nonadditive genetic common factor influences plus additive genetic + shared environmental influences specific to consumption gives a slightly better fit ($x^2_{11} = 14.75, p = 0.19$).

Table 3. Proportions of variance attributable to common factor and specific factor genetic and environmental influences under a bivariate model

	Male like-sex pairs			Female like-sex pairs		
	Consumption (%)		Intoxication (%)	Consumption (%)		Intoxication (%)
Source of variance	Common	Specific	Common	Common	Specific	Common
Nonshared environment	0.4	30.7	57.1	1.1	43.0	61.8
Additive gene action	62.9	6.0	42.9	22.8	16.8	38.1
Shared environment				16.1	0	0.2

Direction of Causation Results

Table 4 summarizes the results of fitting direction of causation models. For female like-sex pairs, the model that specified that increased weekly consumption is a cause of lower intoxication ratings (consumption --> sensitivity) gave a slightly better fit than the alternative model (sensitivity --> consumption), which specified that decreased sensitivity is a cause of increased consumption, but neither model gave a significantly worse fit than the general bivariate model ($\chi^2_2=1.69, p=0.43$; $\chi^2_2=3.60, p=0.17$). From the female like-sex data, we were therefore unable to resolve direction of causation. For male like-sex pairs, the sensitivity --> consumption model, rejected by χ^2 test of goodness of fit, gave a significantly worse fit than the general bivariate model ($\chi^2_2=15.96$, $p<0.001$). The consumption --> sensitivity model gave a good fit to the data, and a fit which was not significantly worse than that of the general bivariate model ($\chi^2_2=4.01, p=0.13$), but which was significantly worse than that of the reciprocal interaction model ($\chi^2_1=4.01$, $p<0.05$). Thus, in males, the two simple direction of causation models were rejected in favor of the reciprocal interaction model.

Parameter estimates under the reciprocal interaction model are given for both male and female like-sex analyses in Table 5. Parameters have been standardized to give unit total variance for each variable. In both sexes, the major causal influence is that of consumption on sensitivity (path i in Fig. 2), and in fact the sign of the reciprocal path i′ is in the opposite direction to what was predicted (i.e., increased sensitivity appears to cause increased consumption). This probably reflects the strong negative correlation between estimates of i and i′ when a reciprocal interaction model is fitted to twin data. Alternatively, it is possible that there is a tendency for those who are especially sensitive to the effects of alcohol but enjoy the feeling of intoxication to have increased consumption. In males, the additive genetic parameter for sensitivity has gone to its lower bound of zero. This implies that the only genetic effects on male sensitivity are those mediated through the path from weekly consumption to sensitivity. In females, all genetic variance in sensitivity appears to be nonadditive, an unlikely result that probably reflects the strong negative correlation between estimates of additive and nonadditive genetic parameters in twin data,[13] which makes it difficult to obtain positive estimates of both additive and nonadditive variance components.

DISCUSSION

We examined the causal relationship between sensitivity to alcohol, as assessed by self-report intoxication after a standard dose of alcohol, and average weekly alcohol consumption (in standard drinks) by using cross-sectional twin data. Subjects were instructed to use the highest

Table 4. Comparison of Goodness of Fit of Direction of Causation Models

	Female like-sex pairs			Male like-sex pairs		
Model	df	x^2	p	df	x^2	p
Consumption → sensitivity	13	16.44	0.23	13	11.22	0.59
Sensitivity → consumption	13	18.35	0.15	13	23.17	0.04
Consumption ↔ sensitivity	12	15.80	0.20	12	7.21	0.84
General model	11	14.75	0.19	11	7.21	0.78

Table 5. Parameter Estimates under Standardized Solution for Reciprocal Interaction Direction of Causation Model

	Consumption			Sensitivity	
Parameter	Males	Females	Parameter	Males	Females
e	0.643	0.694	e′	0.831	0.765
h	0.711	0.774	h′	0.000	0.000
c		0.270	c′	0.179	
d	0.783		d′		0.543
i′	0.364	0.171	i	−0.770	−0.171

See Fig. 2 for explanation of parameters.

intoxication rating if they were "the most drunk they had ever been," an instruction which will have encouraged a comparison with previous occasions when they had been intoxicated. Our measure of sensitivity to alcohol, therefore, was most probably assessing to what degree an individual's maximum ever alcohol consumption was greater than or less than the standard dose given in the experimental protocol. We wished to test whether differences in sensitivity were a cause of differences in habitual consumption (e.g., because an individual's ability to tolerate high levels of alcohol consumption is having a causal influence on average weekly consumption) or whether differences in weekly consumption were a cause of differences in sensitivity.

In males, we found significant genetic effects on both weekly consumption and self-report intoxication. Furthermore, the association between sensitivity to alcohol and habitual level of alcohol consumption was largely genetically determined. However, it appeared that decreased sensitivity was an outcome of increased weekly alcohol consumption, rather than a precursor. Indeed, after taking into account genetic effects on habitual consumption and the causal path from consumption to sensitivity, we found no residual genetic effects specific to sensitivity. These data emphasize the importance of adequately controlling for drinking history in studies that seek to relate sensitivity to alcohol to genetic risk for alcoholism. The strength of the association of self-report intoxication with a simple self-report measure of average weekly consumption (r = 0.53 in males, r = 0.33 in females)[28] also provides an unexpectedly strong validation of that measure, at least for male respondents!

In females, we found a similar trend to that observed in males, with habitual consumption emerging as a likely precursor of decreased sensitivity. However, this trend was not significant. We were not even able to resolve genetic and nongenetic models for the causes of variation in drinking pattern and self-report intoxication in this small sample, although other data have confirmed a significant genetic influence on female habitual consumption pattern.[17,21]

The data analytic methods that we have applied in this paper are applicable to a wide range of problems where there is uncertainty about direction of causation. These methods require that two variables have a relatively strong association: the lower correlation between consumption and intoxication rating in female twins than in males is the most likely cause of our inability to obtain significant results for the female twin pairs. They also require that the two variables have somewhat different modes of inheritance: the twin design provides no information about direction of causation if twin correlations for the two variables are identical.[41,42] When these conditions are satisfied, appropriate analysis of twin data can provide important information about direction of causation in cases where the ideal experiment (e.g., studying the response of alcohol of abstinent subjects) is impracticable or unethical.

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