



GENETIC EFFECTS ON ALCOHOL CONSUMPTION PATTERNS AND PROBLEMS IN WOMEN

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ABSTRACT

We review evidence that genetic factors play no less important a role in the etiology of alcoholism in women than in men. Potential mediators of this genetic influence (differences in personality or alcohol sensitivity) exhibit equal heritability in men and women. Genetically determined differences in alcohol preference (or consumption level), a phenotype widely used in animal models of alcoholism, have been neglected as a mechanism of alcoholism inheritance. Using data from the 1992-3 interview survey of the Australian twin panel (N=5995 twins), we have reexamined the mediating role of personality and alcohol consumption variables. By comparing the non-alcoholic co-twins of alcoholic twins, and twins from concordant unaffected pairs (separately for MZ and DZ pairs), we have avoided the problem of obtaining consumption and personality assessments that are contaminated by history of alcoholism. In MZ pairs, in both genders, co-twin's heavy alcohol exposure (drinking 5+ drinks in one day) and co-twin's Novelty Seeking score, are both predictive of alcoholism in the respondent. The effect of co-twin's heavy alcohol exposure remains significant even when the respondent's personality variables are controlled for, implying that there are genetic effects on alcoholism risk mediated through consumption pattern that are independent of those mediated through personality differences.

KEY WORDS: Alcoholism heritability, gender differences, personality, alcohol consumption

GENETICS AND ALCOHOLISM IN WOMEN

There is a widespread belief that the genetic contribution to alcoholism risk is greater in men than in women (Cloninger, 1987; McGue, 1993). Several factors have contributed to this belief: (i) a failure to recognize that in order to show higher heritability in men than in women, it is not sufficient to demonstrate that only in men does the heritability differ significantly from zero (which can be achieved by studying insufficient numbers of women), but rather that it is necessary to show significant heterogeneity of heritability estimates of alcoholism between men and women; (ii) in analyses of data from alcoholic probands identified through treatment facilities and their relatives, the use of questionable ascertainment corrections, which in effect assume that the degree of genetic risk of alcoholism cases identified through epidemiologic surveys such as the ECA (e.g. Robins and Regier, 1991), which will typically include many mild cases, can be equated to the degree of genetic risk of the probands, which typically will be much more severe cases; (iii) lack of awareness of the imprecision of point estimates of heritability from individual twin or adoption studies (Heath et al., in press).

Data from the largest genetic studies are in fact consistent with equal and in most cases substantial heritability of alcoholism in both genders (see Heath et al., in press, for further details). Consider, for example, the Swedish adoption data of Cloninger et al. (1981). If we estimate the heritability of alcoholism (operationalized as one or more Swedish temperance board registrations), using data from this community sample of biological parents and their adopted-away offspring, without attempting any subclassification into alcoholism subtypes, we find no significant gender differences in the heritability estimates, and obtain a point estimate for the heritability of alcoholism in men and women of 37%, but with a broad confidence interval

(95% CI 19-56%). This estimate is probably an underestimate of true heritability, since it does not correct for the overrepresentation of alcoholics among biological parents who give up their offspring for adoption (i.e. truncation of the lower tail of the distribution of genetic risk). The gender difference in the heritability of alcoholism reported for the Minnesota twin study (McGue et al., 1992), a study of alcoholic twin probands identified through treatment facilities and their co-twins, disappears if we use an ascertainment correction that postulates that only the most severe alcoholics, with higher genetic liability, get into treatment series (Heath et al., in press); but the overall heritability estimate in this study becomes non-significant in both genders! The high heritability for DSM-III-R alcohol dependence found in the Virginia twin study, based on personal interviews with over 1000 female like-sex pairs from a community sample (55%: Kendler et al., 1992), again has a very wide confidence interval (95% CI 0-69%). Our own data from the Australian twin panel (Heath et al., 1994), based on interviews conducted in 1992-3 with 5995 twins, give no significant evidence for higher heritability in men than in women, and yield a heritability estimate for alcohol dependence in men and women of approximately 64% (95% CI 31-72%). While this absence of a gender difference is a consistent finding across studies, differences in the magnitude of heritability estimates are found between community surveys, which have typically obtained heritability estimates in the range 45-65%, and surveys of clinically ascertained samples, which have produced estimates in the range 15-30% (at least under one model for ascertainment correction: Heath et al., 1994c). Possible reasons for this difference may be such factors as barriers to treatment access for alcoholics, or alternatively use of incorrect statistical adjustments for non-random sampling, issues that some researchers seem not to have understood (e.g. Plomin et al., 1994).

HOW DOES THE GENETIC INFLUENCE ON ALCOHOLISM ARISE?

There are a variety of mechanisms by which the genetic influence on alcoholism risk in women (and men) may arise, and it is likely that many of these each account for some small proportion of the total genetic variance in risk. When we consider the various possibilities, we find little that would lead us to anticipate high heritability of alcoholism in men only. Various researchers have proposed an important role of temperament or personality differences in the inheritance of alcoholism risk, notably in Cloninger's (1987) theory of the association between high Novelty Seeking (a measure of impulsivity), low Harm Avoidance (a measure of trait anxiety), low Reward Dependence (a composite measure of social extraversion, dependency and sensibility), and an early-onset 'type II' form of alcoholism that is believed to be highly heritable and found predominantly in men; and between low Novelty Seeking, high Harm Avoidance, high Reward Dependence and a late-onset 'type I' alcoholism that is found in both women and men and exhibits more modest heritability. While our own data from the Australian twin sample confirm substantial heritability of these personality dimensions (accounting for 54-61% of the reliable variance in these measures), these estimates are almost identical in magnitude in women and men (Heath et al., 1994a). We may note, however, that high heritability of anti-social traits, with a much higher proportion of male than female alcoholics exhibiting comorbid anti-social behavior, could generate the predicted difference in heritability.

Alcohol challenge studies of high-risk samples (which have typically been limited to comparisons of male offspring of male alcoholics, and controls) have reported a significant association between high-risk status and decreased subjective intoxication after alcohol challenge (Pollock, 1992), as well as differences in body-sway (Newlin and Thompson, 1990). Recently reported data obtained by Schuckit (1994), from the longitudinal follow-up of his alcohol challenge sample, appear to confirm the association between reduced post-alcohol intoxication (assessed in early adulthood) and subsequent risk of alcohol dependence in men. Data from the Australian Alcohol Challenge Twin Study (AACTS) conducted in 1978-9, a study which used a volunteer twin sample unselected for alcoholism risk, and which included approximately equal numbers of men and women, confirm substantial genetic influences on differences in post-alcohol intoxication, body-sway and psychomotor performance, but do not exhibit any consistent gender differences in the magnitude of those influences (Martin et al., 1985; Heath and Martin, 1992). For those AACTS twins included in the interview survey of the Australian twin panel, we have found a significant association in men between decreased post-alcohol intoxication, and lifetime history of alcohol dependence assessed at the interview follow-up, with a trend in the same direction in women (unpublished data). Although current analyses have not addressed temporal ordering - the onset of alcoholism may have preceded participation in the alcohol

challenge study in some cases - this finding at least emphasizes the importance of studying alcohol challenge performance in women as well as men.

The possibility that some of the genetic influences on alcoholism risk may be mediated through differences in alcohol consumption pattern has largely been neglected in research on humans, despite the fact that alcohol consumption level has been a widely used phenotype in animal models of alcoholism, using rodent strains selected for high or low preference for alcohol (Li, 1990). Data from large epidemiologic twin surveys in the U.S.A., Scandinavia and Australia confirm a significant and substantial genetic contribution to individual differences in alcohol consumption patterns, with the magnitude of that genetic influence in most data-sets comparable in women and men (Heath, 1994). It is natural to question whether such genetic differences contribute to differences in alcoholism risk in non-Oriental populations - an association between ALDH2 isozyme deficiency, decreased alcohol use and decreased alcoholism risk is well established for some Oriental populations, e.g. Japanese: Agarwal and Goedde, 1989. To address this question, we use data from the recent interview survey of the Australian National Health and Medical Research Council twin panel, a volunteer panel mainly of European ancestry.

ALCOHOL RESEARCH IN THE AUSTRALIAN TWIN PANEL

Some 206 twin pairs participated in the original AACT study in 1978-9. Shortly thereafter, in 1980-1, a self-report questionnaire ('1981 survey') was mailed to some 5967 adult twin pairs, aged 17 and older, registered with the twin panel at that period ('1981 cohort'), including 195 pairs from the AACT sample. The survey included general questions about health, personality, attitudes and lifestyle, including items about alcohol consumption pattern but not alcohol-related problems (Jardine and Martin, 1984; Heath et al., 1989, 1991a,b). Completed questionnaires were returned by both members of 3808 pairs (132 pairs from the AACT sample), and by one 'singleton' twin only from an additional 567 pairs (16 pairs from the AACT sample), yielding an overall pairwise response rate of 64% and an individual response rate of 69%. (Questionnaires returned after the completion of the study, by one complete pair and two single twins, have been excluded from these numbers, but would otherwise give a total of 3811 complete pairs and 565 singletons). In 1988-89 an 8-year follow-up mailing of the 3808 pairs where both twins had responded to the 1981 survey was conducted, using a self-report questionnaire that included a short-form of the Tridimensional Personality Questionnaire (Cloninger et al., 1991) as well as questions about alcohol consumption and questions based on Feighner criteria (Feighner et al., 1972) about alcohol problems (Heath and Martin, 1994; Heath et al., 1994a). To maximize response rate, in cases where respondents did not respond to repeated mailings, an option of an abbreviated telephone interview (which included consumption but not problem assessments) was offered. Completed questionnaires or abbreviated interviews were received by both members of 2997 pairs, and by one twin only from 335 pairs, yielding a pairwise response rate of 79% and an individual response rate of 83%. Pairs to whom no questionnaires were mailed because one or both twins were deceased, or not locatable, are included as non-responders in these percentages. A follow-up survey of the 567 singleton twins from the 1981 survey was also piloted, but since address changes for this subgroup had not been updated since the original survey, response rates were poor. Finally, in 1992-3 a telephone interview was conducted with (a) those pairs where at least one twin had responded to the 1989 survey, and (b) all other locatable twins who had participated in the original AACT survey, with responses received from 5995 twins. This total included 349 twins who had participated in the AACT survey (85% response rate), 5879 twins (including 116 AACT twins) who had participated in the 1981 survey (77% response rate) and 5662 twins who had participated in the 1989 survey (89% response rate). Based on a telephone adaptation of the SSAGA (Bucholz et al., 1994), the diagnostic interview developed for genetic research on alcoholism, the survey assessed lifetime history of alcohol dependence and other major DSM-III-R axis I diagnoses.

CONSUMPTION PATTERN, PERSONALITY AND THE GENETIC CONTRIBUTION TO ALCOHOLISM RISK

Assessment of the alcohol consumption patterns of individuals with a history of alcohol dependence can tell us nothing about their mediating role in the inheritance of alcoholism. Personality differences between alcoholics and non-alcoholics may likewise be a consequence of excessive alcohol use, rather than a risk-factor. By testing for differences between the non-alcoholic MZ or DZ co-twins of alcoholic twins (who on average will still have increased genetic liability for alcoholism), and non-alcoholic co-twins from

concordant unaffected pairs, we have avoided this confound. Alcoholism here was operationalized as DSM-III-R alcohol dependence (Heath et al., 1994b). Analyses presented here were limited to data on like-sex pairs. Sample sizes were 60 MZF, 56 MZM, 53 DZF and 54 DZM non-alcoholic twins from discordant pairs, and 1052 MZF, 377 MZM, 557 DZF and 192 DZM twins from concordant unaffected pairs. For the TPQ personality scales, we found significantly elevated Novelty Seeking scores in the monozygotic co-twins of alcoholics compared to non-alcoholics (MZF: 0.51 vs 0.40, $p < 0.001$; MZM: 0.44 vs 0.36, $p < 0.001$), and significantly lower Harm Avoidance scores in monozygotic female co-twins of alcoholics (MZF: 0.36 vs 0.44, $p < 0.001$; MZM: 0.32 vs 0.30, $p = 0.57$). All personality scores were scaled to take values between zero and unity. Differences for dizygotic pairs, and differences for Reward Dependence, were non-significant. Heavy alcohol exposure (drinking at least 5 drinks in a single day) in MZ twins was significantly associated with co-twin's alcoholism risk (MZF: OR 6.81, 95% CI 2.91-15.95; MZM: OR 3.02, 95% CI 1.77-5.14), but in DZ pairs this association was non-significant (DZF: OR 1.54, 95% CI 0.85-2.77; DZM: OR 1.03, 95% CI 0.61-1.73). Heavy alcohol exposure remained a significant predictor even when the respondent's own personality variables were included in a multiple logistic regression analysis (MZF: partial OR 4.64, 95% CI 1.81-11.89, $p = 0.001$; MZM: partial OR 3.63, 95% CI 1.87-7.06, $p < 0.001$).

CONCLUSIONS

Our results suggest that the Novelty Seeking scale does indeed assess one aspect of personality that is associated with increased genetic risk of alcoholism in women as well as men. The analyses presented here do not specifically exclude the possibility of a shared environmental association; however, model-fitting analyses of the twin pair covariances for Novelty Seeking, presented in Heath et al. (1994a), give no evidence for any shared environmental effects on this trait). Although we found that low Harm Avoidance was significantly associated with increased genetic risk of alcoholism in women, we were unable to replicate this finding in men. When interpreting our results, it is important to note that our power to detect a relationship between genetic risk for alcoholism and a potential mediating variable will be in part a function of the magnitude of the genetic covariance between alcoholism and that variable in twin pairs. Since the raw heritability estimates (i.e. uncorrected for measurement error) for the TPQ variables, based on the short 18-item scales that we used in this study, are relatively modest (37-44%), this will make it more difficult to detect a significant relationship.

Our measure of alcohol exposure is perhaps best interpreted as a measure of lack of heavy exposure, i.e. of identifying those individuals who have never had 5 or more drinks of alcohol in a single day and so are at reduced risk of alcoholism. The finding that the proportion of individuals who have never had 5 or more alcoholic drinks is significantly lower among the monozygotic co-twins of alcoholics, and that this association persists even when personality differences are controlled for, implies that in addition to genetic effects mediated through personality, there are genetic effects mediated through consumption pattern, perhaps associated with increased probability of experiencing adverse reactions to alcohol.

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