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An Assessment of the Genetic Relationship Between Alcohol Metabolism and Alcoholism Risk in Australian Twins of European Ancestry

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The present analyses examined genetic influences on alcohol metabolism and their possible relationship to risk of alcohol dependence. Subjects were 206 Australian twin pairs who participated in an alcohol challenge protocol in 1979–1981, in which they were given a 0.75 g/kg dose of alcohol; blood alcohol concentrations (BACs) measured at five times over a 3-hr period after alcohol ingestion were examined. Structural equation modeling, fitting a combined autoregressive and common factor model, indicated significant heritabilities for both men and women (h^2 range = 0.19–0.71), with significant parameter heterogeneity as a function of gender. In 1992–1993, both twins from 159 of the alcohol challenge pairs completed a telephone-administered psychiatric diagnostic interview. Repeated-measures MANOVAs were used to examine whether respondent's or cotwin's DSM-III-R alcohol dependence status, or parental history of alcohol problems, was associated with variation in alcohol metabolism. There was some evidence that individuals at increased genetic risk of alcohol dependence [with either a paternal history of alcohol problems (women) or an MZ male cotwin who reported a history of alcohol dependence by 1992–1993] showed lower initial BACs than other groups. However, this effect was not seen in those who themselves had a history of alcohol dependence by interview follow-up, perhaps because this relationship was already masked by a history of excessive drinking at baseline.

KEY WORDS: Twins; blood alcohol concentration; alcohol metabolism; alcohol dependence; pharmacogenetics.

INTRODUCTION

Genetic Influences on Alcoholism

Many studies have examined the influence of genetic factors on alcohol dependence. Twin and adoption studies involving samples of predominantly European ancestry, which assess genetic and environmental influences by comparing groups that differ in their genetic similarity (e.g., comparing MZ pairs to DZ pairs or comparing risk to offspring of biological versus adoptive parents), have indicated that alcoholism is genetically influenced (for reviews see McGue, 1993, 1994; Heath, 1995; Heath *et. al.*, 1997b). Evidence for a genetic influence on alcohol dependence is particularly strong for men. Heath *et al.* (1997b) noted that heritability estimates from studies linking official alcoholism treatment records and twin/adoption registers and from epidemiologic community-based samples are quite high, ranging from 43 to 63%, whereas heritability estimates from proband-ascertained samples are considerably lower (0–31%). Evidence for women is mixed. Several twin/adoption studies have failed to find

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significant heritability for alcohol dependence in women (Cutrona *et al.*, 1994; Goodwin *et al.*, 1977; McGue *et al.*, 1992; Sigvardsson *et al.* 1996), while other studies have found evidence of significant heritability in women (Cadoret *et al.*, 1985; Cloninger *et al.*, 1985; Heath *et al.*, 1997a), and still others have found evidence for only some alcohol dependence measures (Kendler *et al.*, 1992). Heath and colleagues, in analyses of an Australian sample (Heath *et al.*, 1997a) and in their review of the literature (Heath *et al.*, 1997b), did not find evidence of significantly lower heritabilities for alcohol dependence in women compared to men.

Genetic Effects on Alcohol Metabolism

Twin studies assessing genetic influences on alcohol metabolism in individuals of European ancestry have generally obtained evidence of significant genetic influence on measures of blood alcohol concentration (BAC) and rate of elimination (e.g., Kopun and Propping, 1977; Martin *et al.*, 1985b). In an early twin study, Kopun and Propping (1977) estimated the heritability of alcohol absorption as 0.57 and the heritability of alcohol elimination as 0.46. In analyses of the Australian alcohol challenge data (the same data that are reanalyzed here), Martin *et al.* (1985b) obtained a heritability estimate of 0.62 for peak BAC and a heritability estimate of 0.49 for rate of alcohol elimination. Although one study did not find evidence for genetic influences on BAC at any time, the sample in that study consisted of only 12 MZ and 7 DZ twin pairs (Cobb *et al.*, 1984).

Results from studies assessing the relationship between ADH/ALDH genotypes [which have been found to be associated with differences in alcohol dependence risk in samples of Asian ancestry (e.g., Chen *et al.*, 1996; Higuchi *et al.*, 1994, 1996a, b; Nakamura *et al.*, 1996; Shen *et al.*, 1997; Thomasson *et al.*, 1991, 1994)] and BAC or alcohol elimination measures have been inconsistent. Wall *et al.* (1992) found no differences between flushing and nonflushing subjects on mean BAC or at any of six individual assessments (all of the flushers had at least one ALDH2*2 allele, and none of the nonflushers had any ALDH2*2 alleles). Mizoi *et al.* (1994) found differences in alcohol elimination and peak blood acetaldehyde levels according to ALDH2 genotype but no differences according to ADH2 genotype. Wall *et al.* (1996), using a Native American sample, reported a nonsignificant trend toward subjects with the ADH2*3 allele having faster rates of alcohol elimination than subjects with the ADH2*1 allele.

The Relationship Between Alcohol Metabolism and Alcoholism Risk

Several studies have examined the relationship between alcohol metabolism and alcoholism risk as assessed by family history (Nagoshi and Wilson, 1987; O'Malley and Maisto, 1985; Pollock *et al.*, 1986; Savoie *et al.*, 1988; Schuckit, 1981). In all of these studies, alcohol metabolism of family history positive (FHP) subjects has been compared with that of family history negative (FHN) subjects. Two of the studies assessed BACs (Pollock *et al.*, 1986; Schuckit, 1981); the other three assessed breath alcohol levels (Nagoshi and Wilson, 1987; O'Malley and Maisto, 1985; Savoie *et al.*, 1988). In three of the studies, FHP and FHN subjects were matched for prior alcohol consumption (Nagoshi and Wilson, 1987; O'Malley and Maisto, 1985; Schuckit, 1981); in the remaining two studies, analyses indicated that there were no differences in drinking history between the groups (Pollock *et al.*, 1986; Savoie *et al.*, 1988). Only one of these studies found any evidence of differences in alcohol metabolism according to family history: Nagoshi and Wilson (1987) found significantly higher average breath alcohol concentrations in FHP individuals after their second follow-up dose of alcohol but no differences between FHP and FHN individuals after the initial dose or the first follow-up dose. Other researchers have reported no differences in alcohol absorption or time to peak alcohol concentration (Nagoshi and Wilson, 1987; Savoie *et al.*, 1988; Schuckit, 1981) or for alcohol elimination (Nagoshi and Wilson, 1987; Savoie *et al.*, 1988). Thus, studies that have assessed family history of alcoholism have found little evidence of an association between family history and alcohol metabolism.

Overview

In the present analyses, we have utilized BAC as a measure of alcohol metabolism and examined the relationship between genetic influences on BAC and genetic risk to alcohol dependence. Initially we examined the relative contribution of genetic and environmental factors to repeated BAC assessments. BAC has been analyzed in this sample previously (Martin *et al.*, 1985b), however, their analyses focused on predicted BAC levels, whereas ours involve the actual BAC assessments. Furthermore, advances in structural equation modeling packages have allowed us to test a more general autoregressive model [an autoregressive model is particularly useful for analyzing longitudinal data, as it is one in which a latent factor at time t is thought

to be directly influenced by time $t-1$ in addition to any innovation (for a discussion see Neale and Cardon, 1992).] In the second stage of analyses, we examined the relationship among alcohol metabolism (BAC), parental history of alcohol problems, and respondent and cotwin alcohol dependence. The twin design should give us increased power (compared to FHP/FHN analyses using a family study design) to detect significant genetic covariance between blood alcohol levels and alcohol dependence. The methods that we use are likely to have broad applicability in pharmacogenetic studies where participants are not drug naive, so that the interpretation of conventional bivariate genetic analyses would be uncertain.

METHODS

Sample

Analyses were conducted using a sample of young adult Australian twin pairs which has been described in detail previously (Martin *et al.*, 1985a, b). The subjects, volunteers in an alcohol challenge study conducted between 1979 and 1981, were recruited from the Australian NH & MRC Twin Registry. A small proportion of twins (less than 5%) was unable to complete the protocol (usually because of nausea following the alcohol dose) and was therefore excluded from the study. Two hundred six twin pairs (43 MZM, 37 DZM, 45 MZF, 42 DZF, and 39 DZO pairs) with a mean age of 23.1 years completed the alcohol challenge protocol and were included in the present analyses. All of the twin pairs were of European ancestry. Both members of a twin pair were tested on the same day; two to six pairs were tested together. Zygosity was determined through blood tests. In 1992–1993, 159 of these pairs (33 MZM, 25 DZM, 36 MZF, 35 DZF, and 30 DZO) were interviewed with a structured psychiatric instrument from which a diagnosis of alcohol dependence (DSM-III-R) was obtained. Parental history information on alcohol problems was also obtained from the twins [see Heath *et al.* (1997a) for full details of the interview assessment]. Data from these 159 pairs were examined further to explore the possibility of a genetic correlation between BAC and alcohol dependence.

Procedures

The measures and alcohol challenge protocol, which have been described in detail previously (Martin *et al.*, 1985a, b), are summarized only briefly here. Sessions began 9:00 AM. Subjects were instructed to eat a light, nonfatty breakfast prior to their arrival. Upon their arrival, subjects completed a questionnaire probing, in part, their drinking and smoking history. Subjects were given a breathalyzer test to confirm that their blood alcohol levels were zero before being given a weight-adjusted 0.75 g/kg dose of alcohol. The alcohol was diluted to 10% (v/v) in a sugarless "lemon squash" (a drink that contained lemon juice and soda water). They were instructed to drink the beverage at a steady pace over a 20-min period. BAC analyses were limited to blood alcohol measurements (mg/100 ml) taken at an average of 56, 68, 83, 123, and 182 min postingestion (another assessment, taken at an average of 143 min, was not included in the present analyses because only about half of the subjects were assessed at that time point).

A subsample of alcohol challenge subjects was included in a survey of some 6000 Australian twin pairs in 1992–1993 (Heath *et al.*, 1997a). Alcohol dependence status (DSM-III-R) was evaluated for the twins using an assessment that was adapted for telephone administration from the SSAGA (Bucholz *et al.*, 1994). In the analyses presented here, parental history of alcohol problems was assessed for both biological mother and biological father using a single question from the family history assessment (Slutske *et al.*, 1996): "Has drinking ever caused your (natural) father/mother to have problems with health, family, job or police, or other problems?" For the purpose of these analyses, a parent was identified as having a history of alcohol problems if either member of the pair indicated that there had been problems; paternal and maternal alcohol problems were coded separately [see Slutske *et al.* (1996) for a discussion of the reliability of this item].

The full alcohol challenge sample ($n = 206$ pairs) was used for analyses of BAC; the subsample ($n = 159$ pairs) was used for the analyses relating BAC to alcoholism risk.

Analyses

Preliminary Analyses

A total of 57 individuals met lifetime DSM-III-R criteria for alcohol dependence (33 males and 24 females), including both members of 12 pairs. A diagnosis of DSM-III-R alcohol dependence was used to create seven risk categories from which six dummy variables [ordered here from highest to lowest genetic risk of alcohol dependence (see Heath *et al.*, 1997a)] were created: (i) respondent alcohol dependent, regardless of cotwin's status ($n = 57$); (ii) respondent not

alcohol dependent, MZ cotwin alcohol dependent (n = 13); (iii) respondent not alcohol dependent, female DZ cotwin alcohol dependent (n = 7); (iv) respondent not alcohol dependent, male DZ cotwin alcohol dependent (n = 13); (v) neither respondent nor male DZ cotwin alcohol dependent (n = 53); (vi) neither respondent nor female DZ cotwin alcohol dependent (n = 75); and, for the comparison group, (vii) neither respondent nor MZ cotwin alcohol dependent (n = 100). This parameterization allows us to examine the relationship between BAC and genetic risk of alcohol dependence while avoiding the possible confounding between BAC and alcohol dependence *at baseline* (history of alcohol dependence was not assessed at baseline, and history of alcohol problems was not used as an exclusionary criterion). A significant positive (or negative) genetic correlation between BAC and alcohol dependence risk would predict a progressive decrease (or increase) in BAC among nondependent individuals from highest (ii) to lowest (vii) genetic risk category.

An individual's parent was classified as having a history of alcohol problems if either member of the twin pair indicated that the parent had had alcohol problems. Using this criterion, 43 pairs had a biological father and 10 pairs had a biological mother who had a history of alcohol problems.

Three other baseline variables (obtained from questionnaire data at the time of the alcohol challenge study) were included as covariates in the analyses examining the association between BAC and alcohol dependence: respondent's age, approximate number of lifetime drinking occasions (four subjects were missing this item), and smoking status (one subject was missing this item). Respondents were divided into three age groups, according to their age at the time they completed the alcohol challenge study: 18–19 years (n = 47 males, 49 females), 20–24 years (n = 46 males, 67 females), and 25–34 years (n = 53 males, 56 females). Three alcohol experience groups were created based on the item assessing lifetime drinking occasions: 50 or fewer (n = 20 males, 23 females), 51–500 (n = 51 males, 69 females), and more than 500 (n = 73 males, 78 females). Smoking status in 1979 was analyzed as a dichotomous variable: never/ex-smoker (n = 101 males, 107 females) versus current smoker (n = 44 males, 65 females).

Genetic Analyses of BAC

The statistical package Mx (Neale, 1997) was used for structural equation modeling analyses to examine the pattern of familiality. Models were fitted to the observed raw data by maximum likelihood (Eaves *et al.*, 1978; Neale, 1997). Because of the low power to estimate nonadditive genetic effects, models estimating only additive genetic and nonshared environmental influences were fitted. A first-order autoregressive model was tested first. A second model, containing a common genetic factor in addition to the first-order autoregressive model, was also tested. Both models were compared to a Cholesky model. The fit of the models was tested using likelihood-ratio chi-square tests. The significance of the parameters was determined by estimating 95% confidence intervals (Neale, 1997; Neale and Miller, 1997), and nonsignificant parameters were dropped. Male and female parameters were estimated separately; a model equating their parameters was tested to assess sex differences in the pattern of genetic and environmental influence.

Alcohol Dependence Analyses

Repeated-measures MANOVAs were conducted using SAS (SAS Institute, Inc., 1996) to assess associations among BAC and the alcohol consumption, alcohol dependence, and family history variables. The five BACs were entered as dependent variables. There were 11 independent variables: age group, lifetime drinking occasions category, current smoking status, paternal and maternal alcohol problems, and 6 dummy-coded variables for respondent or cotwin dependence status (always entered jointly in the MANOVA analyses, with MZ pairs concordant for not being alcohol dependent used as the comparison group). The dummy-coded variables for respondent and cotwin alcohol dependence allow for the examination of BAC as a function of genetic risk of alcohol dependence. If there is a significant genetic correlation between BAC and alcohol dependence liability, then we should expect to observe a systematic relationship between BAC and degree of genetic risk of alcohol dependence. MANOVAs were conducted separately for men and women. Because some subjects were missing individual items, the final sample for these analyses included 275 individuals (147 females and 128 males).

RESULTS

Blood Alcohol Concentration

Observed blood alcohol concentration levels (BACs; mg/100 ml) for each assessment are presented by gender in Table I. BACs were higher for females than for males at each assessment; for both groups,

Table I. Mean Observed Blood Alcohol Concentration Levels (mg/100 ml) at Each Assessment

	Mean BAC (SD)	
	Males	Females
Time 1	89.04 (17.70) (n = 192)	95.39 (19.13) (n = 196)
Time 2	88.93 (15.26) (n = 195)	96.69 (17.19) (n = 212)
Time 3	88.95 (15.20) (n = 193)	96.85 (14.65) (n = 194)
Time 4	80.82 (13.31) (n = 199)	89.98 (13.00) (n = 212)
Time 5	67.18 (12.58) (n = 194)	75.40 (11.95) (n = 209)

BACs were relatively stable across the first three assessments, declined somewhat on the fourth occasion, and decreased dramatically at the final time. Intraclass correlations were consistent with a familial contribution to BAC for both males and females (see Table II). For females, the MZ correlations were substantially greater than the DZ correlations at each time, providing evidence of considerable (even potentially nonadditive) genetic influence. For males, the MZ correlations were greater than the DZ correlations for the last four times and were consistent with additive genetic influence in most cases. At the first assessment, the DZ male correlation was substantially greater than the MZ correlation, a pattern that is not consistent with any genetic model. The DZO correlations were quite variable in magnitude: somewhat smaller than the like-sex DZ correlations at the first two assessments (indicative of sex-specific genetic effects) and somewhat greater than the like-sex DZ correlations at the last three times (a pattern that is also not consistent with any simple genetic model).

The initial autoregressive genetic model (i.e., a model implying a simplex structure over time for both the additive genetic and nonshared environmental parameters) had a fit function of 14702.94 (–2 times the log likelihood) with 1930 degrees of freedom (df). The difference between this model and a saturated Cholesky model yielded a $\chi^2 = 49.71$ with 24 df ($p < .01$); indicating that the autoregressive model provided a poorer fit to the data than the more general Cholesky did. The fit of the autoregressive model was significantly improved when a common genetic factor (i.e., a factor containing genetic variance shared at all five times) was included in addition to the autoregressive genetic and nonshared environmental paths ($\chi^2 = 27.61$, df = 10, $p < .05$). The combined autoregressive and common genetic factor model, which was not significantly worse than the saturated Cholesky ($\chi^2 = 22.10$, df = 14, $p = .08$), was selected as the appropriate base model. Male and female parameters could not be equated ($\chi^2 = 124.47$, df = 33, $p < .05$). The final genetic model, once nonsignificant parameters had been dropped, is depicted in Fig. 1a for males and Fig. 1b for females (fit versus full common genetic factor plus autoregressive model: $\chi^2 = 6.25$, df = 13, $p > .50$).

For males, there was strong evidence for an autoregressive pattern of genetic influence; all genetic transmission paths were significant, occasion-specific effects were only present for two of the five assessments, and the common genetic factor only loaded on the first and last occasions. For females, the common genetic factor was much more prominent than the autoregressive pattern: the common factor loaded on four of the five occasions (Nos. 1, 2, 4, and 5), and the only significant transmission path was from the second assessment to the third assessment (the one for which the common factor was not significant). For both males and females, it was necessary to retain the full autoregressive pattern for the nonshared environmental parameters. Proportions of variance attributable to genetic and nonshared environmental factors are presented in Table III. One discrepancy between the intraclass correlations and the proportions of variance attributable to genetic influences warrants further discussion. For the women, the model-fitting analyses indicated markedly lower heritabilities on the fourth and fifth occasions than would have been expected from the correlations. Since these times were the ones with the strongest evidence of nonadditive genetic influence, and sample sizes were small, one should interpret the diminished heritabilities cautiously.

Associations with Alcohol Dependence

Repeated-measures MANOVAs were used to examine which variables were associated with BAC. For females, there were main effects of time since dosing [$F(4,130) = 4.46$, $p < .05$], of neither respondent nor DZF cotwin being alcohol dependent [$F(5,129) = 2.34$, $p < .05$], and of having a biological father with a history of alcohol problems [$F(5,129) = 2.98$, $p < .05$]. The main effect of time since dosing indicated that BACs were relatively stable over the first three occasions, declined somewhat on the fourth occasion, and decreased substantially at the final assessment (see Table I). The other two main effects had to be inter-

Table II. Intrapair Correlations at Each BAC Assessment According to Zygosity

	Intraclass correlation				
	MZF	DZF	MZM	DZM	DZO
Time 1	.73	.23	.36	.68	.11
Time 2	.58	.21	.63	.45	.04
Time 3	.57	.19	.72	.46	.54
Time 4	.50	.01	.36	.02	.37
Time 5	.56	.06	.76	.44	.36

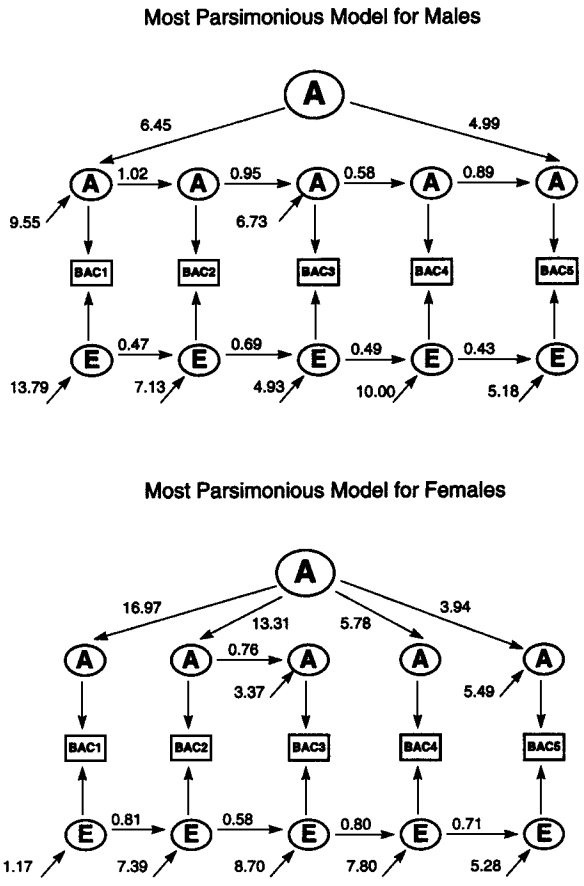

Fig. 1. Most-parsimonious genetic model for males and females. All paths are significant (as determined by 95% confidence intervals).

Table III. Proportions of Variance at Each BAC Assessment Attributable to Additive Genetic and Nonshared Environmental Factors

	Proportion of variance	
	Additive genetic	Nonshared environment
	Males	
Time 1	0.41	0.59
Time 2	0.60	0.40
Time 3	0.71	0.29
Time 4	0.33	0.67
Time 5	0.68	0.32
	Females	
Time 1	0.70	0.30
Time 2	0.56	0.44
Time 3	0.48	0.52
Time 4	0.19	0.81
Time 5	0.32	0.68

preted in terms of their interactions with time since dosing. Examination of the time since dosing × DZF cotwin alcoholism status interaction [$F(4,130) = 2.91$, $p < .05$] indicated that, compared to the other groups (which did not differ significantly), the women who were not alcohol dependent and had a DZF cotwin who also was not dependent ($n = 47$) had slightly higher BACs on the first two occasions and slightly lower BACs at the last three times, although these differences were not significant at any individual time (see Fig. 2). Examination of the time since dosing × paternal alcohol problems interaction [$F(4,130) = 3.35$, $p < .05$] indicated that although the groups showed the same general pattern, the females with a father who had a history of alcohol problems ($n = 33$; 8 of whom were alcohol dependent themselves) had slightly lower initial BACs and had slightly slower decreases in BAC levels. These differences did not reach statistical significance at any individual time point (see Fig. 3).

The MANOVA for males indicated three main effects: an effect of time since dosing [$F(4,111) = 3.14$, $p < .05$], an effect of age group [$F(10,220) = 2.12$, $p < .05$], and an effect of being nondependent with an MZ cotwin who was alcohol dependent [$F(5, 110) = 3.38$, $p < .05$]. The main effect of time since dosing indicated that BACs were relatively stable over the first three oc-

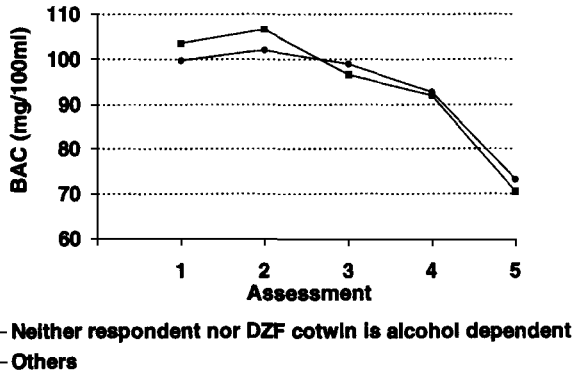

Fig. 2. Interaction between time since dosing and cotwin dependence status in females. Neither respondent nor DZF cotwin alcohol dependent is a low-risk category (n = 47); others includes all other female respondents and is generally a higher-risk category (n = 100).

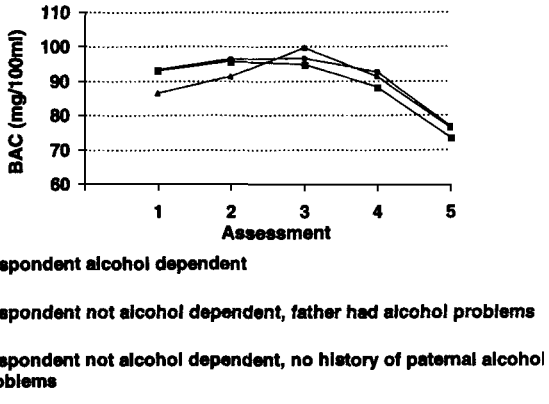

Fig. 3. Interaction between time since dosing and paternal alcohol problems in females. Respondent dependent (n = 19) and paternal alcohol problems (n = 25) are high-risk categories; neither respondent nor father dependent is a lower-risk category (n = 103).

casions, declined slightly at the fourth time point, and declined dramatically at the final time (see Table I). The effect of age group indicated that the oldest cohort (n = 46) had higher BACs than did the younger two cohorts (covariate adjusted mean BACs were 64.72 and 68.07 for the youngest and middle groups, respectively, and 74.00 for the oldest group). The effect associated with being a non-alcohol-dependent respondent with an MZM cotwin who was alcohol dependent had to be interpreted in terms of an interaction between this subgroup and time [$F(4, 111) = 2.80$, $p < .05$]. Although caution should be used in interpreting the interaction (because of the small size of the subgroup; n = 4), examination of this interaction indicated that, compared to the other groups (which did not differ significantly), the individuals who were not alcohol dependent but had an MZ cotwin who was alcohol dependent had significantly lower BACs on the first three occasions than the other respondents but that the BACs at the last two times did not differ between the groups. It also appeared that the individuals in the subgroup had peak BAC levels considerably later than the rest of the respondents. This interaction is depicted in Fig. 4. A similar pattern was seen for the larger group of nondependent twins from the MZ-discordant pairs (n = 7) when pairs who had been dropped from the analysis because of missing data for one or more covariates were added.

DISCUSSION

Consistent with previous studies, the present analyses confirmed that there are significant genetic influences on alcohol metabolism (as measured by BAC) in both men and women: the heritability estimates for men ranged from 0.33 to 0.71 and the estimates for women ranged from 0.19 to 0.70. Although the heritability estimates for men and women were of a similar magnitude, there were indications that the pattern of genetic influence differed according to gender. First, the male and female parameters could not be equated. Second, there was a strong autoregressive pattern of genetic influence for the men, whereas evidence of a common genetic factor was more prominent for the women. Finally, the intraclass correlations for the men were consistent primarily with additive genetic influence, whereas the correlations for the women suggested nonadditive genetic influence. Because the alcohol challenge paradigm is both time-intensive and expensive, the sample size was modest and we did not have sufficient power to test a model containing nonadditive genetic influences. It is also possible that with larger sample sizes we would have detected both common factor and autoregressive effects in both genders.

In contrast to most previous studies, we did find some evidence for a relationship between BAC and family history of alcohol problems. Unexpectedly, however, this relationship was observed only in those who reported no personal history of alcohol problems at interview in 1992–1993. Nondependent women with a paternal history of alcohol problems exhibited lower initial blood alcohol levels and a later (and somewhat higher) peak, differing significantly from dependent women and from nondependent women with no paternal history of alcohol problems, with the latter groups not differing significantly. Nondependent men whose MZ cotwin reported a history of alcohol dependence (and who therefore were on average at increased ge-

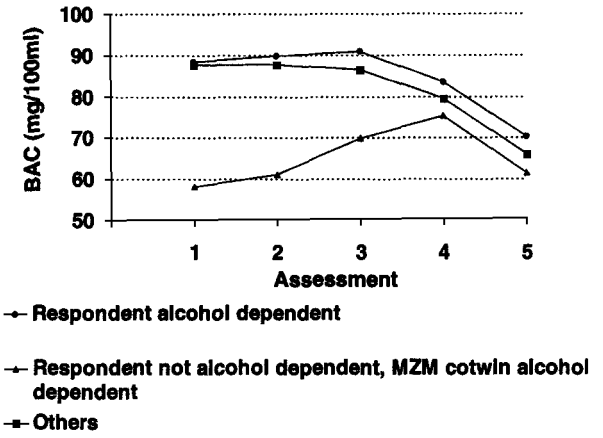

Fig. 4. Interaction between time since dosing and MZM cotwin dependence status in males. MZM cotwin dependent ($n = 4$) and respondent dependent ($n = 32$) are high-risk categories; others includes all other male respondents and is generally a lower-risk category ($n = 92$).

netic risk of alcohol dependence) also showed lower initial blood alcohol levels and a later peak (but also a lower peak in this case). However, we did not see the overall pattern expected based on genetic risk. Furthermore, what we cannot determine is whether the observed differences were behavioral or physiological. A behavioral interpretation of the findings would be that those at increased familial risk who never developed a history of alcohol dependence were merely drinking the standard dose of alcohol relatively late in the 20-min interval when the alcohol had to be consumed (while it would be standard practice today to give a series of measured doses to control for the participants' rate of consumption, this practice was not followed when this early challenge study was conducted). Results are also consistent, however, with the possibility of an underlying metabolic difference, which is masked (perhaps through impaired metabolism because of a history of excessive drinking) in those who developed alcohol dependence (and who indeed may already have had a history of alcohol problems at the time they were tested, since personal history and family history of alcohol problems were not used as exclusionary criteria for the original challenge study). Negative findings in most prior studies comparing family history-positive and family history-negative groups do not preclude the possibility that the effect which we observed was physiological rather than behavioral in origin: our power to detect such effects in a discordant twin pair design is greatly increased. They do, however, point to a need for replication under more rigorously controlled testing conditions.

Several negative findings should also be noted. We did not find an association between alcohol metabolism (as measured by BAC) and experience with alcohol as measured by lifetime drinking occasions (both assessed in 1979–1981). Using the same sample as in the present analyses, Whitfield and Martin (1994) found evidence of a considerable genetic correlation (.36) between weekly alcohol consumption and peak BAC. We selected lifetime drinking occasions over a measure of weekly alcohol consumption because the associations between the observed BACs and the lifetime drinking occasions were marginally higher than the associations between BAC and weekly consumption, particularly for men (using weekly alcohol consumption instead of lifetime drinking occasions in the MANOVAs did not change the results dramatically, although there was a trend toward weekly alcohol consumption being associated with BAC in the women). We also found no association between BAC and smoking status. Madden *et al.* (1995, 1997) found that current smoking status was related to self-reported intoxication after alcohol challenge in this same sample. In addition, both Madden *et al.* (1995) and Kopun and Propping (1977) found that smoking was related faster alcohol elimination in men [Madden *et al.* (1995) found no evidence of a similar effect in women].

In sum, the present analyses provide confirmatory evidence for genetic influences on BAC and raise the possibility of some overlap with genetic influences on alcohol dependence risk, although nonphysiological explanations for our observed findings cannot be ruled out.

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