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Is Alcohol-Related Flushing a Protective Factor for Alcoholism in Caucasians?

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Although alcohol-related flushing seems to be a genetically influenced protective factor for alcoholism in some Asian groups, little is known about whether this is true for Caucasians. The evidence for alcohol-related flushing as a protective factor for the development of alcoholism was examined in a sample of 5831 Australian twins (2041 men, 3790 women) who were administered a structured psychiatric interview. Twin correlations for self-reported adverse alcohol reactions (e.g., "flushing or blushing" and "feeling very sleepy" after drinking 1 or 2 drinks) were modest, suggesting minimal contribution of genetic factors, but when corrected for reliability of measurement, were consistent with moderate heritabilities. In accord with studies examining Asian samples, we found that individuals who experienced adverse reactions after drinking small amounts of alcohol drank less often and slightly less per drinking occasion than those who did not experience adverse reactions. However, those who experienced adverse reactions were *more likely* to have symptoms of alcoholism and to report a parental history of alcohol problems. We conclude that self-reported alcohol-related flushing is not a protective factor for alcoholism in Caucasians and may be a risk factor.

Key Words: Adverse Alcohol Reactions, Flushing, Alcoholism Risk, Twins.

ALTHOUGH THERE is accumulating evidence that genetic influences may account for a substantial portion of the population variation in alcoholism,[1] alcohol-related flushing is one of the few alcohol-related phenotypes that has been associated with a specific genotype in a population. Many individuals of Japanese, Chinese, and Korean descent experience unpleasant symptoms, such as facial flushing and increases in heart rate after drinking small amounts of alcohol.[2] The underlying pathology of this condition has been determined to be a deficiency in the ability to metabolize acetaldehyde derived from alcohol, a deficiency that is strongly associated with whether or not one has inherited a specific allele of aldehyde dehydrogenase (*ALDH2*2*).[3]

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The identification of a gene that is associated with individual differences in the ability to metabolize alcohol, and the consequent effects that one receives from drinking alcohol, indirectly supports the notion that a genotype (*ALDH2*2*) and phenotype (flushing) are protective factors for the development of alcoholism. There is fairly good evidence for this in Asian populations. Studies that have examined the association between the ALDH2 genotype or flushing status and alcohol consumption in Asians, with only a few exceptions,[4–7] have found a significant negative association.[4,5,8–12] It seems that Asians who experience alcohol-related flushing reactions drink less alcohol than those who do not. Studies that have examined the association between the ALDH2 genotype or flushing status and alcohol *problems* (including alcoholism) in Asians have been even more consistent in demonstrating a significant negative association.[8,13–15] Asians who flush are less likely to develop alcoholism than those who do not flush. The evidence supports the proposition that genetically influenced alcohol-related flushing reactions protect against the development of alcoholism in Asian populations.

Caucasians are known to experience alcohol-related flushing reactions, but with a much lower prevalence than is found among Asian groups.[2] The specific alleles that have been identified as important in the etiology of flushing reactions in Asians are nearly nonexistent in Caucasian groups;[16,17] therefore, flushing among Caucasians may be etiologically distinct from that experienced by Asians. Although a specific genotype has not been associated with flushing status in Caucasians, a family study[18] suggests that genetic influences may be important.

Efforts to generalize to Caucasians the significant association between flushing and lower alcohol use found in Asians have yielded more negative[4,6,7,9,19] than positive findings.[20] One study found that Caucasian flushers actually drank more than nonflushers,[21] and another found that the strength and direction of the association depended on the beverage type.[5] We know of no studies to date that have directly examined the association between flushing and alcohol *problems* in non-Asians. An early study of intensity of alcohol-related flushing and family history of alcoholism,[22] however, found that flushing was more intense among young men with a paternal family history of alcoholism than those without such a history, which is opposite to what one would expect if flushing is protective. We

conclude that, on the whole, the evidence for alcohol-related flushing as a protective factor for the development of alcoholism in non-Asians is weak at best.

The purpose of this study was to investigate directly whether alcohol-related flushing is a protective factor for alcoholism in Caucasians (Australians of European ancestry). More specifically, we examined: (1) the prevalence of alcohol-related flushing reactions in a large sample of Caucasians; (2) the relative magnitude of the genetic influences on alcohol-related flushing reactions; (3) the relation between alcohol-related flushing reactions and measures of alcohol consumption; and (4) the relation between alcohol-related flushing reactions, symptoms of alcoholism, and parental history of alcohol problems.

METHODS

Subjects

Subjects were participants in the Australian National Health and Medical Research Council (NH&MRC) twin panel, a volunteer twin registry recruited through the media, schools, and a variety of other sources.[23] Three major alcohol-related surveys have been conducted to date with the NH&MRC sample: a mailed questionnaire survey in 1980–1981,[23] a follow-up mailed questionnaire survey in 1988–1989,[24,25] and a telephone interview survey conducted in 1992–1993. Data obtained from the telephone interview survey were primarily analyzed for the present study, and data from the other alcohol-related surveys of the NH&MRC were used to supplement the interview data.

Telephone interviews were attempted with any twin pairs where at least one twin responded to the 1988–1989 mailed questionnaire survey or who had participated in an earlier alcohol challenge study conducted in 1978–1979.[26–28] Telephone interviews were completed with 5995 individuals: 2087 men (mean age 42.7 years, range 28–89) and 3908 women (mean age 44.7 years, range 27–90). Among respondents to the 1988–1989 survey, the response rates for the telephone interview survey were 87.5% among men and 90.6% among women. Excluded from analysis were 46 men (2.2%) and 118 women (3.0%) who reported lifetime abstention from alcohol. The final sample size thus included 5831 individuals (2041 men, 3790 women).

The racial composition of the NH&MRC twin panel is representative of Australia. Immigration practices through the early 1960s encouraged migration of individuals of European (mainly Northern European) descent, so that, for example, at the 1976 census (about the time when the twin registry was formed), <2% of the population was from any Asian country (including Lebanon, China and Hong Kong, India, Sri Lanka, Malaysia, and Vietnam), and only 0.2% were from China or Hong Kong.[29] Thus, the sample is largely Caucasian, and very few subjects are of Asian descent.

Measures

The Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) interview,[30] originally developed for the Collaborative Study on the Genetics of Alcoholism, was modified for use as a telephone interview in Australia. Interview assessments of alcohol use included frequency of alcohol consumption in the last 12 months and quantity of alcohol consumed per drinking occasion (typical amount in the last 12 months, maximum amount in a single day in the last 12 months, and maximum amount in lifetime). Individual alcoholism symptoms as reported at the interview were aggregated into the nine DSM-III-R[31] alcohol dependence criteria by computer algorithm. Parental history of alcohol problems, for the purposes of this study, was assessed by a single item that was asked for both the respondent's father and mother: "Has drinking ever caused your (natural) father/mother to have problems with health, family, job, or police, or other problems?" Because family history of alcohol problems was not obtained by directly interviewing parents, we refer to this measure as an index of *perceived* parental history of alcohol problems.

We used a self-report measure of adverse alcohol-related flushing reactions adapted from the SSAGA interview. Respondents were asked whether they had experienced six specific adverse reactions after drinking 1 or 2 drinks of alcohol. These included: (1) flush or blush—that is, your face and hands felt hot and your face turned red; (2) break out into hives; (3) feel very sleepy; (4) have nausea; (5) have headaches, or head pounding, or throbbing; and (6) have heart palpitations, where your heart beat so hard you could feel it? Positive responses to these questions were followed by asking the respondent if the adverse symptom was *always* experienced after drinking 1 or 2 drinks of alcohol. Based on their responses to questions about each of the six alcohol reactions, subjects were categorized as having "never," "sometimes," or "always" experienced each of the six reactions. In addition, a composite "any adverse alcohol reaction" variable was created; and again, subjects were categorized as "never," "sometimes," and "always" experiencing any adverse alcohol reaction. Because of the structure of the interview items, individuals who were classified as "always" having any alcohol reaction were those who always had the same alcohol reaction every time that they drank, rather than at least one (of any of the six reactions) every time that they drank; respondents were not asked the latter question.

Previous research suggests that the majority of the variables in the present study (i.e., alcohol consumption, alcoholism symptoms) can be measured with reasonable levels of reliability and validity. However, evidence concerning the reliability and validity of the central variable, self-reported adverse reactions to alcohol, is scant, and the limited available evidence suggests that both may be rather low among Caucasians. In a combined sample of 40 young men of Japanese origin and 20 young men of European origin, self-reported frequency of flushing after alcohol correlated only −0.22, with change in skin reflectance of the neck and face (reduced reflectance results from increased blood flow to the skin) 20 min after alcohol.[32] The reliabilities of *objectively measured* physiological reactions to alcohol are also low.[33] The test-retest reliability of skin temperature 20 min after a standard dose of alcohol was 0.41 in 36 women and 0.19 among 46 men,[27] and the 1-month test-retest reliabilities of body temperature change and heart rate change 10 min after alcohol were 0.32 and 0.13 in a combined sample of 18 women and 16 men.[33] We know of no published reports of the reliability of *self-reported* adverse reactions to alcohol.

To estimate the reliability and validity of self-reported adverse alcohol reactions, as well as to examine the consistency of several key analyses, data from other studies using the NH&MRC twin registry were also used in the present study. Facial skin temperature change 20 min after a standard dose of alcohol (0.75 g/kg body weight) was obtained for 348 interviewed subjects (161 men, 187 women) who participated in an alcohol challenge study in 1979–1980[26–28] (Table 1). This provided an assessment of the validity of self-reported "flushing" as an indicator of skin temperature change after drinking among Caucasians. Self-reported adverse alcohol reactions assessed by questionnaire were available for 311 interviewed subjects (142 men, 169 women) who participated in a follow-up of the alcohol challenge study in 1990–1992[20,34] (Table 1). In the follow-up study, subjects were asked to respond "always," "sometimes," and "never" to a global question about their response to alcohol: "Do you experience unpleasant reactions, such as flushing of the face or body, itching, drowsiness, or palpitations after drinking a small amount of alcohol (say, 1 or 2 drinks)?" Although the questions in the SSAGA interview and the alcohol challenge follow-up study were slightly different, the overlap between the two studies provided a rough estimate of the test-retest reliability of self-reported adverse reactions to alcohol in a largely Caucasian sample.

Data from two other large questionnaire surveys of the NH&MRC twin registry were used to examine the consistency of results of the association between adverse alcohol reactions and alcohol use and alcohol problems. Frequency of alcohol consumption in the past year was obtained for 5214 interviewed subjects who were assessed by a mailed questionnaire in

Table 1. Summary of Data from the Australian NH&MRC Twin Registry Used in the Present Study

Year	Study	*n*	Variables used in present study
1992–1993	SSAGA interview	5831	Adverse reactions to alcohol Alcohol consumption DSM-III-R[31] alcohol dependence symptoms Perceived parental alcohol problems
1980–1981	Questionnaire survey[23]	5214	Alcohol consumption
1988–1989	Questionnaire survey[24,25]	4907	Alcohol problems
1979–1980	Alcohol challenge[26–28]	348	Skin temperature change after alcohol
1990–1992	Questionnaire follow-up of alcohol challenge[20,34]	311	Adverse reactions to alcohol

Note: Numbers refer to the number of subjects available for the present study (i.e., those who were not lifetime alcohol abstainers and had participated in the 1992–1993 interview study), not the total sample size for the referenced study.

1980–1981[23] (Table 1). Lifetime alcohol problems were obtained for 4907 interviewed subjects who responded to a mailed questionnaire in 1988–1989[24,25] (Table 1).

Data Analysis

Two main approaches were used to examine the relation between adverse alcohol reactions and alcohol consumption and alcohol problems. First, we ignored the twin structure of the dataset, and compared individuals classified as "never," "sometimes," and "always" experiencing an adverse reaction to alcohol. For ordinal variables, such as frequency of alcohol consumption, reaction groups were compared with the χ^2 test. For quantity of alcohol consumption (a continuous variable), data were first log-transformed to reduce the positive skew of the distribution of scores and then groups were compared by ANOVA. Because the nonindependence of observations from twin pairs leads to an underestimate of the sampling variance of parameter estimates, type I error rates may be inflated when twins are treated as individual subjects in analyses. We used a conservative approach in correcting for this potential bias by recalculating all test statistics by approximating the number of *independent* observations as the original sample size divided by two.

A second strategy compared twin pairs discordant for always experiencing an adverse reaction to alcohol in a case-control analysis. Because twin pairs are perfectly matched for age and race, case-control analyses of alcohol use in twin pairs discordant for adverse alcohol reactions avoids these potential confounds. For dichotomous variables, affected twins (those who always experienced adverse reactions to alcohol) and their unaffected cotwins were compared using McNemar's test. For continuous variables, groups were compared with the matched pair *t* test.

Correlations between adverse alcohol reactions were estimated by the polychoric correlation (or correlation in liability),[35] which is used when one assumes that there is a normally distributed latent variable (e.g., liability to "flushing") that explains an observed ordinal variable (in this case, the categories of "never," "sometimes," and "always"). In other words, we made the assumption that the reaction categories differed in degree rather than in kind and that those who reacted "sometimes" were intermediate (between those who reacted "never" and "always") in their liability to experience adverse alcohol reactions. This assumption can be tested by comparing the observed frequencies in a two-way contingency table (such as that produced by cross-classifying reaction status of twins with their co-twins) with the frequencies expected, assuming a bivariate normal distribution of the variables.[36] We present the results of these χ^2 tests, although they should not be overinterpreted, because the statistical power to detect deviations from bivariate normality in ordinal data is low.[37]

The polychoric correlation was also used to assess the test-retest reliability and monozygotic (MZ) and dizygotic (DZ) twin pair resemblance of adverse reactions to alcohol. To provide a rough estimate of the magnitude of any genetic influences on reactions to alcohol, the heritability was calculated as twice the difference between the MZ and DZ twin correlations. This provides an estimate of the proportion of the *total* variance in the liability to experience adverse alcohol reactions that is due to genetic factors. In addition, the heritability was divided by the estimated test-retest reliability of self-reported adverse alcohol reactions to determine the proportion of the *reliable* variance that can be attributed to genetic factors.

The validity of self-reported "flushing" was computed as the polyserial correlation between self-reported adverse alcohol reactions and skin temperature change after alcohol measured some 12–14 years earlier.

RESULTS

Prevalence of Alcohol-Related Flushing Reactions

Prevalences of the six self-reported alcohol reactions and any alcohol reaction for men and women are presented in Table 2. As expected, the prevalences were relatively low in this mainly Caucasian sample. The least common alcohol reaction was "hives," which affected <1% of men and women. The most common reaction in women was "flushing or blushing" (8.4% always experienced this after drinking a small amount), and the most common reaction among men was "feeling very sleepy" (3.1%). We also found that, overall, adverse alcohol reactions were more commonly experienced by women than men [any alcohol reaction: $\chi^2_{(2)} = 146.53$, $p < 0.001$]. Women were more likely to "flush or blush" [$\chi^2_{(2)} = 202.64$, $p < 0.001$], "feel very sleepy" [$\chi^2_{(2)} = 34.50$, $p < 0.001$], and "have headaches" [$\chi^2_{(2)} = 22.08$, $p < 0.001$] after drinking. These gender differences remained even after using a conservative statistical correction for the nonindependence of observations from twin pairs. There were no significant gender differences in the rates of self-reported "hives," "nausea," or "heart palpitations" after drinking small amounts of alcohol.

Table 3 shows the intercorrelations among the six alcohol reaction items for men and women. All of the items were positively correlated, and the magnitude of the correlations was modest to moderately large. With few exceptions, the intercorrelations were larger in magnitude in men than in women, which suggests that the interview items better identified a flushing syndrome among men and that aversive alcohol reactions among women may be multifactorial. Because the prevalences of many of the alcohol reactions were low, yielding small sample sizes for group comparisons, we focused the remaining analyses on the two most common alcohol reactions, "flushing or blushing," "sleepy," and the composite "any alcohol reaction" variable.

Table 2. Lifetime Prevalences of Self-Reported Adverse Reactions in Australian Men and Women

	Flush	Hives	Sleepy	Nausea	Headache	Heart palpitations	Any
Men *n*	2033	2039	2039	2038	2039	2035	2038
% Sometimes	13.1	0.4	23.8	5.7	9.5	2.7	32.5
% Always	2.2	0.1	0.3	0.3	0.6	0.1	5.5
Women *n*	3762	3776	3774	3774	3774	3772	3775
% Sometimes	23.6	0.8	23.6	7.0	12.4	2.8	38.1
% Always	8.4	0.3	6.8	0.7	1.6	0.6	14.0

Table 3. Polychoric Correlations between Self-Reported Adverse Alcohol Reactions in Australian Men and Women

	Flush	Hives	Sleepy	Nausea	Head-ache	Heart palpitations
				n = 2029		
Flush	—	0.53	0.43	0.41	0.34	0.48
Hives	0.38	—	0.25	0.39	0.44	0.53
Sleepy	0.39	0.37	—	0.54	0.50	0.45
Nausea	0.23	0.23	0.32	—	0.58	0.63
Headache	0.32	0.26	0.44	0.63	—	0.47
Heart palpitations	0.32	0.17	0.36	0.42	0.50	—
				n = 3756		

Note: Men are above diagonal, and women are below diagonal.

Table 4. Twin Correlations and Test-Retest Reliabilities for Self-Reported Adverse Alcohol Reactions in Australian Men and Women

	n	Flush	Sleepy	Any reaction
Twin correlation				
MZ males	384	0.40 (0.10)	0.30 (0.08)	0.38 (0.07)
DZ males	231	0.28 (0.12)	0.11 (0.10)	0.24 (0.09)
MZ females	885	0.33 (0.05)	0.19 (0.05)	0.31 (0.04)
DZ females	506	0.20 (0.07)	0.17 (0.07)	0.13 (0.06)
DZ female/male	584	0.11 (0.07)	0.17 (0.06)	0.19 (0.06)
Reliability	311	0.58 (0.07)	0.46 (0.07)	0.58 (0.06)

Note: SEs are in parentheses. For twin correlations, *n* is the number of twin pairs.

Reliability and Validity of Self-Reported Adverse Alcohol Reactions

The polychoric correlations between the global adverse alcohol reaction questionnaire item and the "flushing," "feeling very sleepy," and any alcohol reaction variables from the SSAGA interview were 0.58, 0.46, and 0.58, respectively (Table 4). These reliabilities are modest, especially in relation to those found for other self-reported alcohol use behaviors.[30,38,39]

The polyserial correlations between skin temperature change after a challenge dose of alcohol and the "flushing," "feeling very sleepy," and any alcohol reaction variables from the SSAGA interview were all essentially 0 (0.00, 0.01, and 0.03, respectively). It may be that the documented variability of physiological changes after alcohol from occasion to occasion[33] may attenuate any association with other variables. Nevertheless, these results suggest that self-reported "flushing" among Caucasians is a misnomer, in that it does not seem to be associated with objectively measured increases in skin temperature after alcohol.

Twin Correlations

Twin correlations for male and female MZ and DZ twins, as well as opposite-sex twin pairs are presented in Table 4. Twin similarity for the alcohol reactions was modest. Although the MZ correlations consistently exceeded the DZ correlations, the MZ-DZ differences were also rather modest, suggesting that the genetic influences on self-reported alcohol reactions in Caucasians are slight, perhaps accounting for 20–30% of the total variance in the liability to experience adverse reactions after drinking alcohol. However, the percentage of *reliable* variance accounted for is in the range of 40–50%. Thus, the relative magnitude of the genetic influences on adverse alcohol reactions among Caucasians seems to be moderate.

Of 18 correlations in liability presented in Table 4, there was no instance in which the cell frequencies in the observed two-way contingency table were inconsistent with a bivariate normal distribution. Therefore, there is no evidence from these data to suggest that our assumption of a normally distributed latent "liability to experience adverse reactions to alcohol" variable underlying the response categories of "never," "sometimes," and "always" is incorrect.

Relation Between Alcohol-Related Flushing Reactions and Measures of Alcohol Consumption

Figure 1a shows the frequency of alcohol consumption for men and women who "never," "sometimes," and "always" experienced any adverse alcohol reaction. In both men and women, those who "always" experienced any adverse alcohol reaction were less likely to have used alcohol more often than once/week over the past year than those who "sometimes" or "never" experienced reactions. Rather, those who experienced alcohol reactions were more likely than those who do not to be infrequent drinkers (once/month or less often) [men: $\chi^2_{(4)} = 73.04, p < 0.001$; women: $\chi^2_{(4)} = 117.09, p < 0.001$]. These group differences were also found for the specific adverse reactions of "flush or blush" and "feeling very sleepy." All of the significant associations between any and specific adverse reactions to alcohol and frequency of alcohol use remained statistically significant, even after using a conservative statistical correction for the nonindependence of observations from twin pairs. To rule out many possible confounding variables, these analyses were repeated in a case-control design using twin pairs discordant for always experiencing any adverse alcohol reaction and the specific adverse reactions of "flushing or blushing" and "feeling very sleepy." The same

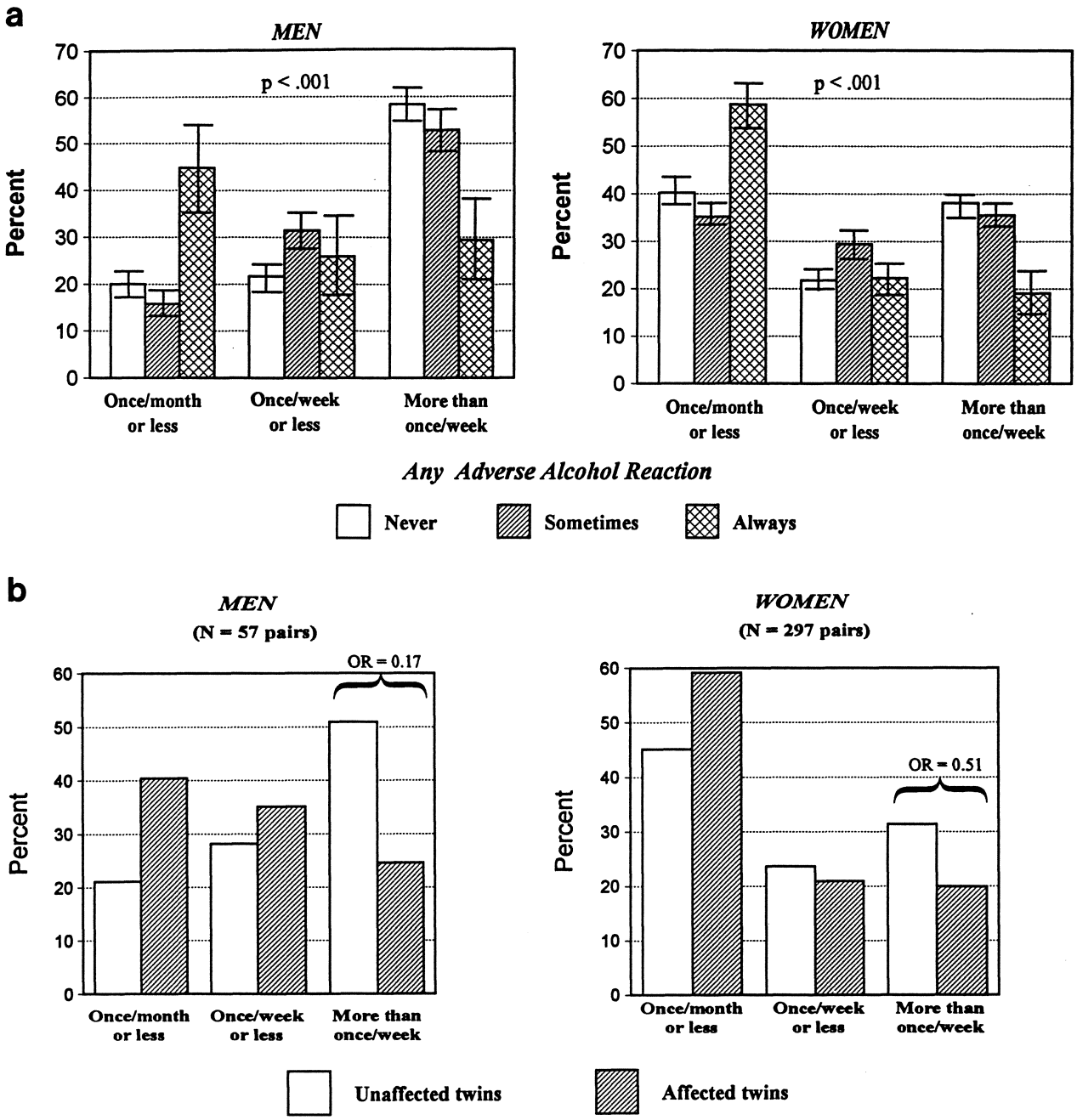

Fig. 1. (a). Frequency of alcohol consumption in the past year in Australian men and women who "never," "sometimes," and "always" experience any adverse alcohol reaction after drinking. Frequency categories are mutually exclusive: once/week or less = more than once/month, but no more than once/week. Bars represent 95% CIs for percentages. Results of χ^2 tests are presented. (b) Frequency of alcohol consumption in the past year in twin pairs discordant for always experiencing any adverse alcohol reaction after drinking. Frequency categories are mutually exclusive: once/week or less = more than once/month, but no more than once/week. Matched pair OR is the ratio of the odds of an affected twin (one who always experiences an alcohol reaction) relative to the odds of an unaffected twin for drinking more than once/week. ORs for both men and women are statistically significant at $p < 0.05$. Note that the OR does not reflect the relative frequency of more than weekly drinking in the two groups, because the figure percentages are based on all of the twin pairs discordant for always experiencing any adverse alcohol reaction, whereas the matched pair OR is based on the subsample of those twin pairs who were also discordant for drinking more than once/week. Matched pair OR compares the frequency of frequent drinking in the affected twin, but not the unaffected twin with the frequency of frequent drinking in the unaffected twin, but not the affected twin.

pattern emerged in the case-control analyses (Fig. 1b); twins who "always" experienced any adverse alcohol reaction were less likely to drink more than once/week than their unaffected cotwins [men: matched-pair odds ratio (OR) = 0.17, 95% confidence interval (CI) = 0.03–0.57; women: OR = 0.51, 95% CI = 0.33–0.77; see Fig. 1b]. When the number of discordant twin pairs were adequate, the results were similar for the specific adverse alcohol reactions of "flush or blush" [men: OR = 0.25, 95% CI = 0.01–2.53; women: OR = 0.53, 95% CI = 0.29–0.93] and "feels very sleepy" [men: OR = 0.17, 95% CI = 0.02–0.75; women: OR = 0.53, 95% CI = 0.29–0.93].

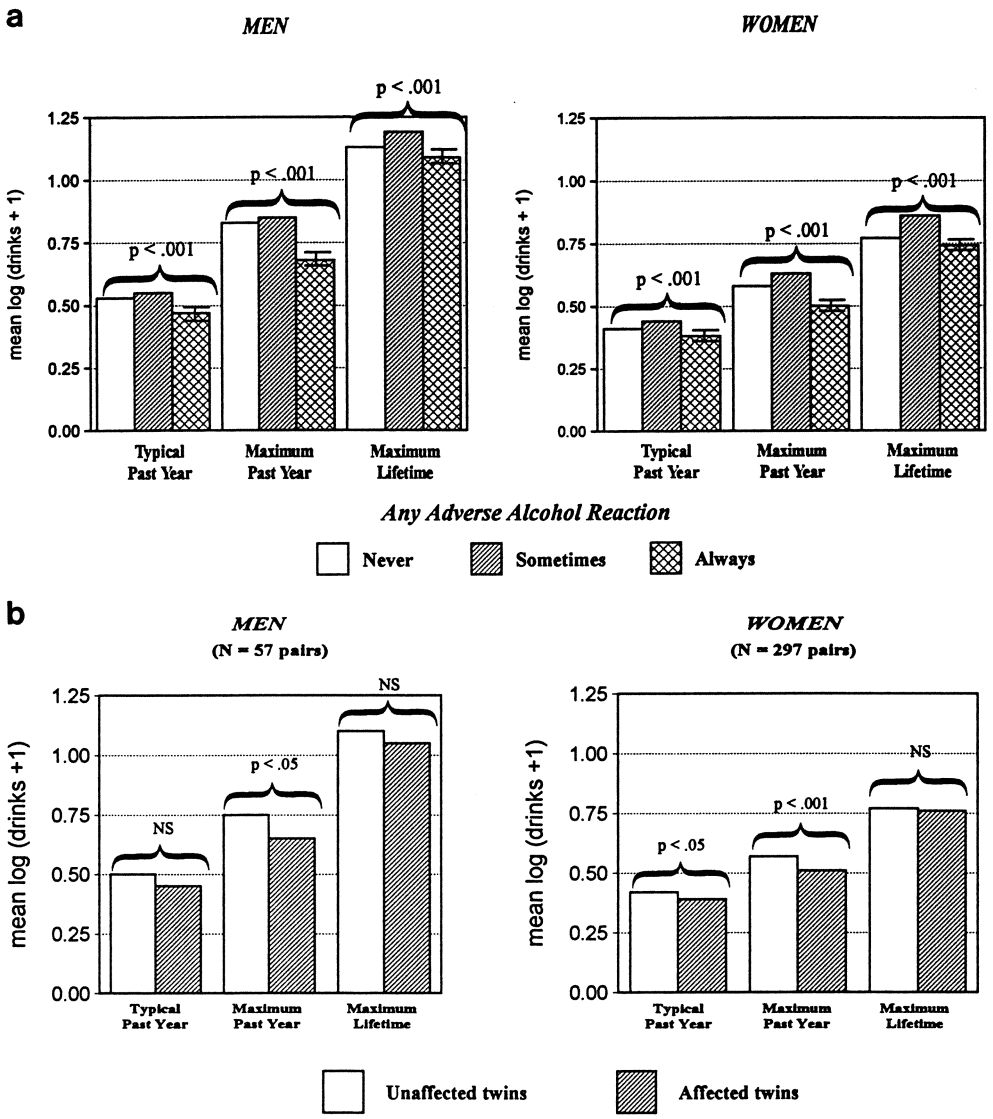

Fig. 2. (a) Mean quantity of alcohol consumption in Australian men and women who "never," "sometimes," and "always" experience any adverse alcohol reaction after drinking. Bars represent SEs; SEs for "never" and "sometimes" groups are too small to graph. Results of ANOVAs are presented. (b) Mean quantity of alcohol consumption in twin pairs discordant for always experiencing any adverse alcohol reaction after drinking. Results of matched pair *t* tests are presented. NS, not statistically significant at the level of $p < 0.05$.

When we examined the frequency of alcohol use over the past year assessed by a mailed questionnaire survey of these subjects *12 years before the interview*, we found the same results: less frequent drinking in 1981 in those who reported in 1993 that they experienced reactions after drinking. (All associations were statistically significant at the level of $p < 0.001$. After correction for the nonindependence of twin pairs, they were still statistically significant at $p < 0.05$).

Figure 2a shows the quantity of alcohol consumed per drinking occasion for men and women who "never," "sometimes," and "always" experienced any adverse alcohol reaction after drinking. For all three indices of alcohol consumption (typical amount of alcohol consumed per drinking occasion in the past year, maximum amount consumed in the past year, and maximum amount ever consumed), those who "always" experienced any adverse alcohol reaction drank less than those who "never" and "sometimes" experienced any adverse alcohol reaction after drinking. The same results were found when we examined differences in the quantity of alcohol consumption between those who "never," "sometimes," and "always" experienced the specific adverse reaction of "feeling very sleepy" after alcohol. When we compared groups classified by whether they "flush or blush," the differences for the typical amount consumed in the past year were not statistically significant after conservative statistical correction for the nonindependence of observations from twin pairs, although group differences for the other consumption measures (maximum amount consumed in the past year and over the lifetime) were. Overall, those who "always" experienced adverse reactions after drinking typically drank one-fourth to two-thirds of a standard drink less per occasion in the last year than those who "never" experienced adverse reactions. The lifetime and past year maximum number of drinks consumed in a single occasion for those who "always" experienced adverse reactions was 1–3 drinks less than those who "never" experienced adverse reactions after drinking.

We attempted to confirm the association between any

Table 5. Lifetime Prevalences of DSM-III-R[31] Alcohol Dependence Symptoms in Australian Men and Women Who "Never," "Sometimes," and "Always" Experience Any Adverse Alcohol Reaction after Drinking

	Men			Women		
	Any adverse alcohol reaction			Any adverse alcohol reaction		
DSM-III-R alcohol dependence symptom	Never	Sometimes	Always	Never	Sometimes	Always
1. Substance taken in larger amounts/over longer period than intended	43.5	56.5	48.7	18.2	28.3	15.2
2. Persistent desire or 1+ unsuccessful efforts to cut down	18.7	31.1	37.8	7.3	14.2	11.8
3. Great deal of time spent using or recovering from effects of alcohol	4.6	11.9	9.9	0.9	3.0	2.3
4. Frequent intoxication/withdrawal symptoms when expected to fulfill major responsibilities or when hazardous	35.3	44.1	40.0	7.5	14.0	9.0
5. Important social/occupational activities given up	2.8	6.8	6.3	0.6	1.5	1.5
6. Continued use despite recurrent social/psychological/physical problems	10.5	19.3	25.2	2.1	5.8	4.1
7. Tolerance	19.1	25.5	16.5	5.7	8.4	6.3
8. Withdrawal	1.3	3.6	6.3	0.3	0.9	1.5
9. Drinking for withdrawal relief	1.9	4.1	7.3	0.7	1.0	1.0

Note: Where prevalences are underlined, the χ^2 test with 2 degrees of freedom was statistically significant at the level of $p < 0.05$, using a conservative correction for the nonindependence of observations from twin pairs (dividing the sample size by two). For ease of interpretation (when the groups differed by the χ^2 test), the lowest rate is single underlined, and the highest rate is double underlined.

and specific adverse alcohol reactions and quantity of alcohol consumption using discordant twin pairs. The results of matched pair *t* tests for any adverse alcohol reaction are presented in Fig. 2b. Although we consistently found that the twin who always experienced adverse alcohol reactions drank slightly less than their unaffected co-twin, few of these differences were statistically significant among the men, perhaps because of the relatively small sample sizes for these analyses (57 male pairs discordant for any adverse alcohol reaction, 19 male pairs discordant for "flush or blush," and 35 male pairs discordant for "feels very sleepy"). In women (297 female pairs discordant for any adverse alcohol reaction, 176 female pairs discordant for "flush or blush," and 172 female pairs discordant for "feels very sleepy"), there were statistically significant differences between groups for both "past year" indices of quantity of alcohol consumption (typical and maximum) for any alcohol reaction and "feels very sleepy." The differences between the "flush or blush" groups were not statistically significant (for any of the alcohol quantity indices), nor were any of the group comparisons for the maximum quantity of alcohol ever consumed (grouping by any alcohol reaction, "flush or blush," or "feels very sleepy").

Relation Between Alcohol-Related Flushing Reactions, Symptoms of Alcoholism, and Family History of (Parental) Alcohol Problems

In Table 5, we present the lifetime rates of DSM-III-R alcohol dependence symptoms in men and women who "never," "sometimes," and "always" experienced any alcohol reaction after drinking. Even after using a conservative statistical correction for the nonindependence of observations from twin pairs, we found that the groups differed for 8 of the 9 alcohol dependence symptoms in men, and for 5 of the 9 symptoms in women. In every case where there was a statistically significant group difference in the rates of alcohol dependence symptoms among men, the group that "never" experienced an alcohol reaction had the *lowest* lifetime prevalence of the symptom, and those who "sometimes" or "always" experienced a reaction had the highest lifetime prevalences. Among women, this was true for 4 of the 5 symptoms for which there were statistically significant group differences. In no instance did those who "never" experienced any adverse reaction to alcohol have a higher rate of an alcohol dependence symptom than the other two reaction groups. Similar results were found when we examined the specific reactions of "flush or blush" and "feels very sleepy."

When we looked at the association between self-reported adverse reactions to alcohol and lifetime alcohol problems assessed by a mailed questionnaire survey of these subjects *3 years before the interview*, we found either no group differences, or in most cases where there were differences, lower rates of alcohol problems in those who reported (in 1993) that they "never" experienced adverse alcohol reactions.

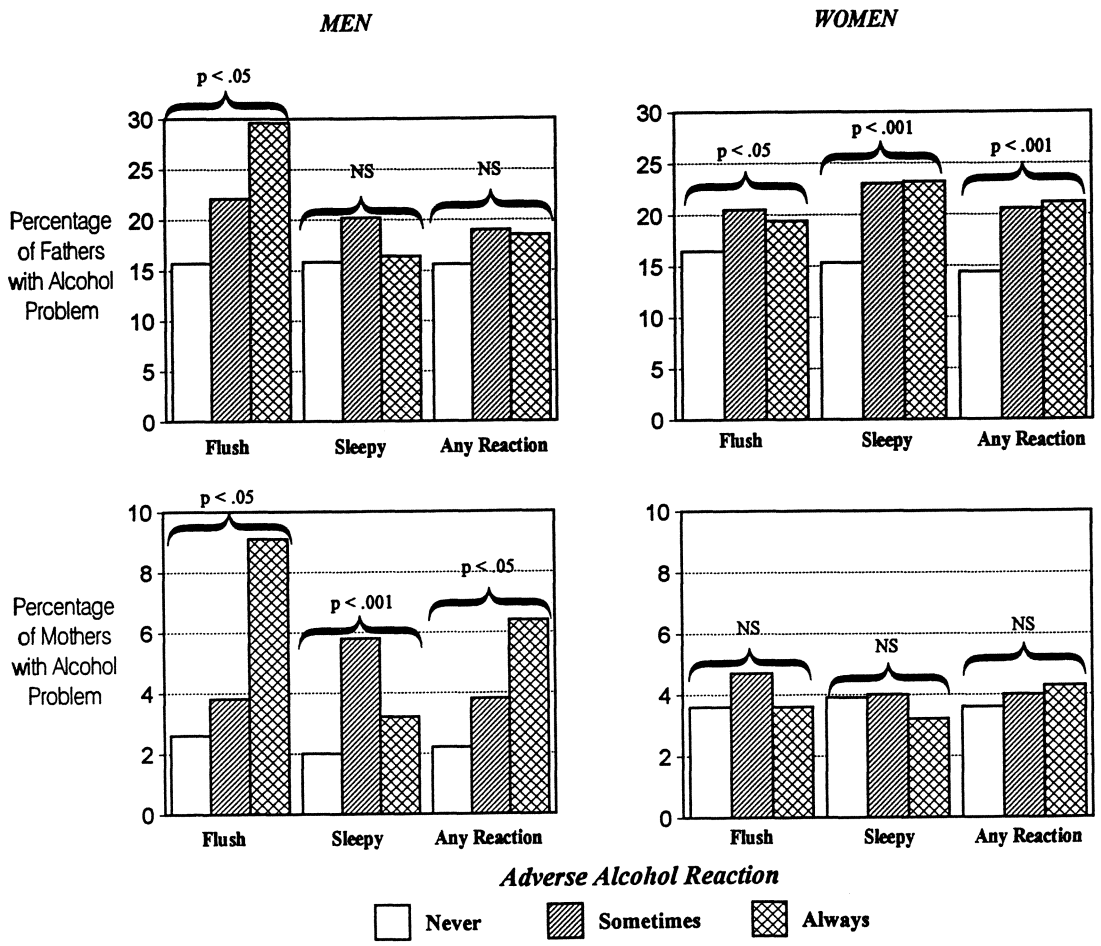

Fig. 3. Rates of perceived paternal and maternal alcohol problems in Australian men and women who "never," "sometimes," and "always" experience "flushing or blushing," "feeling very sleepy," or any adverse alcohol reaction after drinking. Results of χ^2 tests are presented. NS, not statistically significant at the level of $p < 0.05$.

To examine the role of alcohol-related flushing further as a protective factor for the development of alcoholism in Caucasians, we compared the rates of perceived paternal and maternal alcohol problems in individuals who reported that they "never," "sometimes," and "always" experienced adverse reactions to alcohol (Fig. 3). After using a conservative statistical correction, only three of the group differences in parental alcohol problems remained: the rate of maternal alcohol problems in men classified by whether they "felt very sleepy" after drinking [$\chi^2_{(2)} = 9.22$, $p < 0.01$], the rate of paternal alcohol problems in the women grouped according to the any alcohol reaction variable [$\chi^2_{(2)} = 12.58, p < 0.002$], and the specific reaction of "feels very sleepy" [$\chi^2_{(2)} = 15.72$, $p < 0.001$]. In all instances where there were statistically significant group differences, individuals who "never" experienced an alcohol reaction had a *lower* rate of perceived family history of alcohol problems than the other two groups.

DISCUSSION

In a large, community sample of mainly Caucasian individuals, we examined the role of alcohol-related flushing reactions as a protective factor for the development of alcoholism. Many of our findings were consistent with this proposition. Individuals who experienced symptoms, such as flushing, blushing, sleepiness, headaches, or nausea after drinking small amounts of alcohol, drank less frequently in the past year. They tended to drink slightly less alcohol per drinking occasion than those who did not suffer from these effects. Association of adverse reactions to alcohol with frequency of alcohol consumption was quite robust, whether frequency of alcohol consumption was reported at the interview, or it was reported back in 1980–1981, some 12 years earlier. Association of adverse reactions with quantity of alcohol consumption was much weaker and probably only detectable because of the large sample sizes in the present study. Thus, our results confirm earlier findings that have demonstrated an association between experiencing alcohol-related flushing reactions and reduced alcohol consumption in Caucasians,[20] and suggest that previous failures to find such an association, especially when using indicators of quantity of alcohol consumption, may have been due to low statistical power.

Although those who experienced adverse reactions to alcohol *drank less* than those who did not, they were *more*

likely to have lifetime symptoms of DSM-III-R alcohol dependence. When we examined reported rates of alcohol problems in the parents, we found no group differences, or differences that would suggest that alcohol-related flushing reactions are a *risk* factor for alcoholism, rather than a *protective* factor, in that those who experienced adverse reactions were more likely than those who did not to report that their fathers or mothers had alcohol problems. This replicates earlier work by Schuckit and Duby,[22] who found that sons of alcoholics had more intense flushing responses than sons of nonalcoholics. Associations between adverse alcohol reactions and higher rates of alcohol problems and parental alcohol problems were not as robust as those between alcohol reactions and lower alcohol use, and thus must be interpreted with caution. Nevertheless, taken together, the findings of reduced alcohol consumption but increased rates of alcohol problems in "flushers" compared with "nonflushers" are perplexing. We consider several explanations.

To reconcile decreased rates of alcohol use with increased rates of alcohol problems in those who experienced adverse reactions to alcohol, the pattern of alcohol use may need to be considered. In other words, even though those who experience adverse reactions drink less alcohol overall than those who do not experience adverse reactions, they may be more likely to engage in patterns of alcohol consumption that are associated with problems. There was some evidence in our data to suggest that, especially among men, subjects who experienced adverse reactions to alcohol were more likely to have had drinking binges (episodes where they drank for a couple of days or more without sobering up), compared with subjects who did not experience adverse reactions to alcohol.

We must also consider whether some of the individuals who reported adverse alcohol reactions may have been problem drinkers earlier in their lifetime, but more recently tempered their levels of drinking in response to the unpleasant symptoms that they experienced with alcohol. Perhaps "flushing" does not protect one against alcohol problems, but rather protects one against persistent and chronic drinking problems. The availability of questionnaire data on these subjects back in 1980–1981 allowed us to confirm that the frequency of alcohol use was lower in "flushers" than "nonflushers" some 12 years ago, but does not rule out the possibility that there may have been a period of excessive alcohol use before this. With more careful inspection of the timing of specific lifetime alcohol dependence symptoms retrospectively reported at the 1992–1993 interview, we should be able to examine this issue.

Another possible explanation is that alcohol dependence symptoms may be endorsed with the adverse reactions in mind. For example, because of experiencing adverse reactions to alcohol, "flushers" may be more likely to endorse symptoms such as having a persistent desire to cut down on drinking or to perceive themselves as suffering from alcohol problems. Alternatively, individuals who drink despite presumably aversive reactions to alcohol may actually be more vulnerable to the long-term adverse consequences of drinking, perhaps because they are more sensitive to the positive effects of alcohol, or are more prone to develop alcohol tolerance and craving. For example, Whitfield and Martin[34] found that individuals who experienced adverse alcohol reactions were more sensitive to the intoxicating effects of alcohol than those who did not experience adverse reactions. Thus, even though "flushers" may not drink as much or as often as "nonflushers," when they do drink, they may become more intoxicated.

There is continuing debate over whether *increased* or *decreased* sensitivity to the effects of alcohol are predictive of future alcohol problems[40,41] Pomerleau et al.[42] have theorized that individuals who are especially vulnerable to the development of nicotine dependence are those who initially show a greater sensitivity to both the aversive, as well as the positive effects of nicotine. Dependence develops in those who continue to use nicotine at levels to become sufficiently tolerant to the aversive affects, especially in relation to the magnitude of the pleasurable effects of nicotine. Similarly, individuals who continue to drink alcohol regularly despite aversive effects, such as flushing, may eventually reach a point where the enhanced pleasurable effects outweigh the aversive effects. In Caucasians, especially, the flushing response may not be sufficiently aversive to outweigh the positive effects that are received from drinking alcohol. Even in Asian subjects, flushers who had the *ALDH2*2* allele had a more positive subjective response to an alcohol challenge than nonflushers.[43] Flushers may be at a greater risk for developing alcoholism because, in addition to deriving more negative effects from drinking alcohol, they may also derive more positive alcohol effects than nonflushers; these enhanced positive effects might be mediated by increased levels of acetaldehyde. Wall et al.[44] speculate that very small increases in acetaldehyde after drinking (such as that found in Caucasian "flushers" compared with Caucasian "nonflushers") may be associated with an increased risk of developing alcoholism, whereas large increases in acetaldehyde after drinking (such as that found in Asian flushers compared with Asian nonflushers) is associated with a decreased risk of developing alcoholism.

It is very likely that Caucasians who report experiencing adverse reactions after drinking alcohol are a heterogeneous group. Most are deterred from heavy drinking, whereas others apparently are not. It remains for further research to characterize the heterogeneity among self-reported "flushers" and to identify those variables that distinguish "flushers" who are deterred from heavy drinking from those who are not. An intriguing possibility, suggested by Reich and Li,[45] is that traits such as impulsivity may moderate the association between flushing and alcohol use and abuse. Although aversive alcohol reactions may deter most from drinking alcohol, this may not be true for those

high on impulsivity. These individuals may be at especially high risk of developing alcoholism.

Interestingly, self-reported adverse reactions to alcohol in our Australian sample were only of moderate reliability and were not associated with objectively measured skin temperature change after alcohol. Although this lack of association might be attributed to the long time span between our assessment of self-reported adverse reactions and skin temperature change, the findings are consistent with other reports, suggesting low reliabilities and validities for similar measures over much shorter time spans.[27,32,33] Twin correlations for self-reported adverse alcohol reactions were modest, suggesting a minimal contribution of genetic factors (accounting for 20–30% of the total variance), but when corrected for reliability of measurement, were consistent with moderate heritabilities (accounting for 40–50% of the reliable variance). Although a single gene has not been associated with adverse alcohol reactions among Caucasians, it seems that genetic influences are important; however, the additive effect of many genes may influence the characteristic response to small amounts of alcohol in Caucasians. The environmental influences that account for the remaining 50–60% of the reliable variance in the liability to experience adverse alcohol reactions are yet to be determined.

Whether or not alcohol-related flushing proves to be a genetically influenced *risk* factor for alcoholism in Caucasians, the results of this study are very clear on one issue. We found no evidence to suggest that flushing *protects* against the development of alcoholism in non-Asian individuals.

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