GENETIC VARIATION IN ALCOHOL DEHYDROGENASE AND THE BENEFICIAL EFFECT OF MODERATE ALCOHOL CONSUMPTION ON MYOCARDIAL INFARCTION

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ABSTRACT

Background A polymorphism in the gene for alcohol dehydrogenase type 3 (*ADH3*) alters the rate of alcohol metabolism. We investigated the relation among the *ADH3* polymorphism, the level of alcohol consumption, and the risk of myocardial infarction in a nested case–control study based on data from the prospective Physicians' Health Study.

Methods We identified 396 patients with eligible newly diagnosed cases of myocardial infarction among men in the Physicians' Health Study. Of these patients, 374 were matched with 2 randomly selected control subjects each and the remaining 22 with 1 control each (total, 770 controls). The *ADH3* genotype ($\gamma_1\gamma_1$, $\gamma_1\gamma_2$, or $\gamma_2\gamma_2$) was determined in all subjects. We examined the relations among the level of alcohol intake, the *ADH3* genotype, and plasma high-density lipoprotein (HDL) levels in this study population and in a similar cohort of women.

Results As compared with homozygosity for the allele associated with a fast rate of ethanol oxidation (γ_1), homozygosity for the allele associated with a slow rate of ethanol oxidation (γ_2) was associated with a reduced risk of myocardial infarction (relative risk, 0.65; 95 percent confidence interval, 0.43 to 0.99). Moderate alcohol consumption was associated with a decreased risk of myocardial infarction in all three genotype groups ($\gamma_1\gamma_1$, $\gamma_1\gamma_2$, and $\gamma_2\gamma_2$); however, the *ADH3* genotype significantly modified this association (P=0.01 for the interaction). Among men who were homozygous for the γ_1 allele, those who consumed at least one drink per day had a relative risk of myocardial infarction of 0.62 (95 percent confidence interval, 0.34 to 1.13), as compared with the risk among men who consumed less than one drink per week. Men who consumed at least one drink per day and were homozygous for the γ_2 allele had the greatest reduction in risk (relative risk, 0.14; 95 percent confidence interval, 0.04 to 0.45). Such men also had the highest plasma HDL levels (P for interaction = 0.05). We confirmed the interaction among the *ADH3* genotype, the level of alcohol consumption, and the HDL level in an independent study of postmenopausal women (P=0.02).

Conclusions Moderate drinkers who are homozygous for the slow-oxidizing *ADH3* allele have higher HDL levels and a substantially decreased risk of myocardial infarction. (N Engl J Med 2001;344:549-55.)

I N epidemiologic studies, moderate consumption of alcohol is consistently associated with a reduced risk of myocardial infarction; however, the mechanism underlying this association is unclear.[1-6] Some have suggested that the apparent benefit may reflect socioeconomic or lifestyle factors correlated with alcohol consumption, or it may be due to constituents of alcoholic beverages other than ethanol.

The pharmacokinetics of alcohol metabolism has been well studied. The class I alcohol dehydrogenase (ADH) isoenzymes, encoded by *ADH1*, *ADH2*, and *ADH3*, oxidize ethanol and other small, aliphatic alcohols.[7,8] *ADH2* and *ADH3* have polymorphisms that produce isoenzymes with distinct kinetic properties; to date, no functional polymorphisms have been identified in *ADH1*.[7] Among white populations, variant alleles are relatively uncommon at the *ADH2* locus (they are present in less than 10 percent of the population) but common at the *ADH3* locus (present in 40 to 50 percent).[7] At the *ADH3* locus, the γ_1 allele differs from the γ_2 allele by two amino acids at positions 271 and 349.[9] Pharmacokinetic studies show a 2.5-fold difference in the maximal velocity of ethanol oxidation between the homodimeric γ_1 isoenzyme (associated with a fast rate) and the homodimeric γ_2 isoenzyme (associated with a slow rate).[7]

This difference is thought to affect the rate of oxidation of blood ethanol,[7] although the *ADH3* polymorphism had no apparent effect on blood alcohol levels in a short-term study of high-dose alcohol consumption in humans.[10] Epidemiologic studies have associated the *ADH3* polymorphisms with alcohol-associated diseases, such as alcoholism ($\gamma_2\gamma_2$),[11] alcohol-related end-organ damage ($\gamma_1\gamma_1$),[12] and oropharyngeal cancer ($\gamma_1\gamma_1$).[13]

We evaluated the hypothesis that the effect of moderate alcohol consumption on the risk of myocardial infarction would vary according to the *ADH3* genotype. In addition, we assessed the relation among the *ADH3* genotype, the level of alcohol consumption,

and plasma levels of high-density lipoproteins (HDLs) in a group of men and in a similar cohort of women.

METHODS

Study Design

In 1982, the Physicians' Health Study commenced as a randomized, double-blind, placebo-controlled trial of aspirin and beta carotene among 22,071 U.S. male physicians between the ages of 40 and 84 years who had no history of myocardial infarction or stroke.[14] Informed consent was obtained from all subjects, and the research protocol was approved by the institutional review board at Brigham and Women's Hospital in Boston. Before randomization, each subject was asked to provide a blood sample. Specimens were received from 14,916 (68 percent) of the physicians, who form the base-line cohort for this study; collection methods have been described elsewhere.[15] At the time of blood sampling, information was also collected on risk factors for cardiovascular disease.

The men were followed by means of annual mailed questionnaires. We sought the medical records of all men who reported a myocardial infarction so as to confirm that the event met World Health Organization criteria.[16] Sudden deaths that were not confirmed as being due to coronary disease and silent infarcts were excluded. We routinely obtained information on the cause of death from death certificates, medical records, and autopsy reports. Follow-up data on fatal and nonfatal outcomes were obtained for 99 percent of the subjects.

By 1994, 396 men with eligible cases of myocardial infarction had been identified. We attempted to match each patient to two control subjects who were free of myocardial infarction at the time of the diagnosis of myocardial infarction in the patient. Control subjects were randomly selected from among the subjects who sent blood samples and were matched to the patient for age (within one year), smoking status (never smoked, past smoking, or current smoking), and time since randomization (according to six-month intervals). Controls were selected randomly from the same population from which the patients were derived in order to minimize the chance of false positive results due to population stratification (i.e., the selection of controls from a population with a different prevalence of alleles than that of the population of patients). In the case of 22 patients, we could identify only 1 control who met the matching criteria, yielding a total of 1166 subjects (396 patients and 770 controls).

We assessed the relation among the *ADH3* genotype, the level of alcohol consumption, and plasma levels of HDL in an independent study of 325 postmenopausal women who were not taking hormone-replacement therapy. These women were participants in a nested case–control study of breast cancer among the 33,826 subjects in the Nurses' Health Study who had donated blood in the period from 1989 through 1990, as described elsewhere.[17]

Laboratory Analysis

We used the polymerase-chain-reaction assay and restriction-fragment–length polymorphism analysis to determine in a blinded fashion the *ADH3* genotype of each subject.[18] Both negative and positive controls were included. Total cholesterol and HDL cholesterol were measured in the Lipid Research Laboratory of Brigham and Women's Hospital, as described previously.[19]

Statistical Analysis

We used a chi-square test to determine whether the *ADH3* genotypes were in Hardy–Weinberg equilibrium.[20] We used conditional logistic regression to estimate the multivariate relative risks (and 95 percent confidence intervals) of myocardial infarction associated with alcohol intake and the three *ADH3* genotypes. To control for potential confounding, we adjusted for the following risk factors for myocardial infarction in the multivariate models: level of alcohol consumption (<1 drink [approximately 14 g of alcohol] per week, ≥1 drinks per week but <1 drink per day, or ≥1 drinks per day);

body-mass index (defined as the weight in kilograms divided by the square of the height in meters) (≤23.01, >23.01 to 24.40, >24.40 to 26.40, or >26.40); frequency of vigorous (enough to work up a sweat) physical activity (<1, 1 to 4, or ≥5 times per week); presence or absence of hypertension, diabetes, and angina at the time of enrollment; presence or absence of a history of myocardial infarction in a parent before the age of 60 years; and presence or absence of random assignment to aspirin use. Six subjects (four patients and two control subjects) who were taking medication for high cholesterol levels were excluded from all the analyses, and six subjects (one patient and five control subjects) with missing information on alcohol consumption were excluded from the analyses that pertained to alcohol.

We also used conditional logistic regression to assess whether the *ADH3* genotypes modified the relation between the level of alcohol consumption and the risk of myocardial infarction by including interaction terms for each category of alcohol consumption and each *ADH3* genotype. To test for interactions between the level of alcohol consumption and the *ADH3* genotype, we used a likelihood-ratio test to compare nested models that included terms for all combinations of the *ADH3* genotype and levels of alcohol consumption with models without such terms. The P value for trend was based on the Wald test.

We also assessed whether the *ADH3* genotype modified the relation between the level of alcohol consumption and HDL levels. We used mixed regression models to calculate the mean adjusted HDL levels. One patient whose HDL level was more than three interquartile ranges above the median was excluded. In addition to the previously mentioned risk factors for myocardial infarction, we also adjusted for age (as a continuous variable) and smoking status (never, past, or current). For the analyses of 325 women from the Nurses' Health Study, we adjusted for age (<61.5 or ≥61.5 years), body-mass index (<22, 22 to <25, 25 to <29, or ≥29), whether or not blood had been obtained after an overnight fast, whether or not hormone-replacement therapy had been used in the past, and pack-years of smoking (to 1990). Because the average levels of alcohol consumption were lower among the women than among the men, the categories of alcohol consumption were dichotomized (<half a drink per day [<7 g per day] or ≥half a drink per day [≥7 g per day]). Tests for interaction and trend were determined as described previously.

RESULTS

As compared with the control subjects, patients who had had a myocardial infarction had a higher prevalence of diabetes (P=0.01), angina (P<0.001), and hypertension (P<0.001) and were more likely to have a parent who had had a myocardial infarction before the age of 60 years (P=0.05). In addition, patients consumed less alcohol (P=0.02), participated less often in vigorous exercise (P=0.002), and had higher total cholesterol levels (P<0.001) and lower HDL levels (P<0.001).

Among the 14,916 study subjects who provided blood at base line, 93 percent were white. The frequencies of *ADH3* alleles among the control subjects in this study population were 60 percent for the γ_1 allele and 40 percent for the γ_2 allele, results that were consistent with previously reported estimates for whites.[7] The distribution of *ADH3* genotypes among the controls was in Hardy–Weinberg equilibrium (P=0.47). The percentage of controls in each genotype subgroup who consumed at least one drink per day was similar: 30 percent among those who were homozygous for the γ_1 allele ($\gamma_1\gamma_1$), 32 percent among those

who were heterozygous ($\gamma_1\gamma_2$), and 29 percent among those who were homozygous for the γ_2 allele ($\gamma_2\gamma_2$).

As previously reported in this cohort, we found a lower risk of myocardial infarction among men who consumed alcohol daily than among those with lower levels of alcohol intake.[3] As compared with men who consumed less than one drink per week, men who consumed at least one drink per week but less than one drink per day had a multivariate relative risk of myocardial infarction of 0.96 (95 percent confidence interval, 0.70 to 1.32) and men who consumed at least one drink per day had a risk of 0.62 (95 percent confidence interval, 0.43 to 0.91) (P for trend=0.02).

We observed a reduction in the risk of myocardial infarction among men with at least one γ_2 allele. As compared with men who were homozygous for the γ_1 allele, men who were heterozygous had a multivariate relative risk of 0.83 (95 percent confidence interval, 0.62 to 1.11) and men who were homozygous for the γ_2 allele had a risk of 0.65 (95 percent confidence interval, 0.43 to 0.99) (Table 1). In the multivariate analysis, the trend toward a decreasing relative risk from the $\gamma_1\gamma_1$ group to the $\gamma_2\gamma_2$ group was statistically significant (P for trend=0.04). The multivariate relative risks were not affected by adjustment for the level of alcohol consumption.

The *ADH3* genotype significantly modified the effect of the level of alcohol consumption on the risk of myocardial infarction (P=0.01 by the likelihood-ratio test) (Table 2). As compared with the reference group

of men who consumed less than one drink per week and who were homozygous for the γ_1 allele, men who consumed one or more drinks per day had a reduced risk of myocardial infarction regardless of their *ADH3* genotype. However, the reduction in risk was largest (86 percent) among the subgroup of men who drank daily and who were homozygous for the γ_2 allele (multivariate relative risk, 0.14; 95 percent confidence interval, 0.04 to 0.45). A reduction in the risk of myocardial infarction was also observed in the subgroup of men who consumed less than one drink per week and who were homozygous for the γ_2 allele; however, this reduction was not statistically significant (multivariate relative risk, 0.59; 95 percent confidence interval, 0.28 to 1.23; P=0.16). When the level of alcohol consumption was dichotomized (≥ 1 drinks per day or <1 drink per day), the risk of myocardial infarction was lowest among the men who consumed at least one drink per day and who were homozygous for the γ_2 allele (Fig. 1).

There was no evidence to suggest a three-way interaction among the *ADH3* genotype, the level of alcohol consumption, and the use of aspirin treatment on the risk of myocardial infarction among the patients in whom a myocardial infarction occurred before January 1988, when the aspirin component of the trial was terminated (and their matched controls) (P=0.60).

We also assessed the relation among *ADH3* genotype, the level of alcohol consumption, and plasma levels of HDL among 385 patients and 385 controls;

TABLE 1. RELATIVE RISKS OF MYOCARDIAL INFARCTION ACCORDING TO THE *ADH3* GENOTYPE.

VARIABLE	*ADH3* GENOTYPE			P VALUE*
	$\gamma_1\gamma_1$	$\gamma_1\gamma_2$	$\gamma_2\gamma_2$	
No. of subjects (%)				
Patients	161 (41)	184 (46)	51 (13)	
Controls	279 (36)	361 (47)	130 (17)	
Relative risk (95% CI)†				
Matched	1.0‡	0.90 (0.69–1.17)	0.72 (0.50–1.05)	0.09
Multivariate	1.0‡	0.81 (0.61–1.09)	0.64 (0.43–0.98)	0.03
Multivariate, with adjustment for alcohol consumption§	1.0‡	0.83 (0.62–1.11)	0.65 (0.43–0.99)	0.04

*The P value is for the test for trend.

†In the matched analysis, patients and controls were matched for age (within one year), smoking status (never smoked, past smoking, or current smoking), and time since randomization (in six-month intervals). In the multivariate analyses, in addition to adjustment for age, smoking status, and time since randomization, the analyses were adjusted for body-mass index ($\leq$23.01, >23.01 to 24.40, >24.40 to 26.40, or >26.40), frequency of vigorous physical activity (<1, 1 to 4, or $\geq$5 times per week), presence or absence of a family history of myocardial infarction, presence or absence of random assignment to aspirin use, and presence or absence of a history of hypertension, diabetes, and angina at enrollment. Four patients and two controls who were taking medication for high cholesterol levels were excluded. CI denotes confidence interval.

‡This group served as the reference group.

§The categories of alcohol consumption were as follows: <1 drink per week, $\geq$1 drinks per week but <1 drink per day, and $\geq$1 drinks per day. One patient and five controls were excluded because of missing information on alcohol consumption.

TABLE 2. RELATIVE RISKS OF MYOCARDIAL INFARCTION ACCORDING TO
THE *ADH3* GENOTYPE AND THE LEVEL OF ALCOHOL CONSUMPTION.*

LEVEL OF ALCOHOL CONSUMPTION	ADH3 GENOTYPE		
	$\gamma_1\gamma_1$	$\gamma_1\gamma_2$	$\gamma_2\gamma_2$
<1 Drink per week			
No. of patients	50	50	17
No. of controls	78	82	43
Relative risk (95% CI)†			
Matched	1.0‡	0.96 (0.58–1.61)	0.66 (0.34–1.31)
Multivariate	1.0‡	1.01 (0.58–1.75)	0.59 (0.28–1.23)
≥1 Drinks per week but <1 drink per day			
No. of patients	80	82	29
No. of controls	115	163	49
Relative risk (95% CI)†			
Matched	1.06 (0.66–1.69)	0.77 (0.49–1.21)	0.97 (0.55–1.72)
Multivariate	1.11 (0.67–1.84)	0.66 (0.40–1.08)	1.02 (0.55–1.88)
≥1 Drinks per day			
No. of patients	30	52	5
No. of controls	84	114	37
Relative risk (95% CI)†			
Matched	0.55 (0.31–0.97)	0.72 (0.44–1.18)	0.23 (0.08–0.62)
Multivariate	0.62 (0.34–1.13)	0.68 (0.40–1.15)	0.14 (0.04–0.45)

*$P=0.01$ by the likelihood ratio test for the interaction between the *ADH3* genotype and the level of alcohol consumption after adjustment for the factors used for matching and the listed risk factors.

†One patient and five control subjects were excluded because of missing data on alcohol consumption. In the matched analysis, patients and controls were matched for age (within one year), smoking status, and time since randomization (in six-month intervals). In the multivariate analysis, in addition to adjustment for age, smoking status (never smoked, past smoking, or current smoking), and time since randomization, the analyses were adjusted for body-mass index (≤23.01, >23.01 to 24.40, >24.40 to 26.40, or >26.40), frequency of vigorous physical activity (<1, 1 to 4, or ≥5 times per week), presence or absence of a family history of myocardial infarction, presence or absence of random assignment to aspirin use, and presence or absence of a history of hypertension, diabetes, and angina at enrollment. Four patients and two controls who were taking medication for high cholesterol levels were excluded. CI denotes confidence interval.

‡This group served as the reference group.

HDL levels were not measured for the other controls. For all three *ADH3* genotypes, the mean adjusted HDL level among men who had at least one drink per day (47.4 mg per deciliter [1.2 mmol per liter]) was 3.5 mg per deciliter (0.09 mmol per liter) higher than that among men who consumed less than one drink per day (43.9 mg per deciliter [1.1 mmol per liter], $P=0.002$). When the HDL levels were analyzed according to the *ADH3* genotype, the mean adjusted HDL levels were higher among men who consumed at least one drink per day in all three genotype groups (Fig. 2A). However, among these men, HDL levels were highest among those who were homozygous for the γ_2 allele, intermediate among the heterozygotes, and lowest among those who were homozygous for the γ_1 allele ($P=0.05$ for the interaction between the level of alcohol consumption and the genotype on the HDL level). The trend in the HDL level among the genotypes in the group of men who consumed at least one drink per day was significant (P for trend$=0.007$).

The *ADH3* genotype appeared to have no effect on the HDL levels among the men who consumed less than one drink per day. Among the men whose HDL levels were measured, the significant reduction in the risk of myocardial infarction associated with homozygosity for the γ_2 allele was still present after adjustment for HDL levels. As compared with men who consumed less than one drink per week and who were homozygous for the γ_1 allele, men who consumed at least one drink per day and who were homozygous for the γ_2 allele had a multivariate relative risk of myocardial infarction of 0.15 (95 percent confidence interval, 0.05 to 0.46) before adjustment for base-line HDL levels and a risk of 0.23 (95 percent confidence interval, 0.07 to 0.77) after adjustment.

We found a similar relation among the *ADH3* genotype, the level of alcohol consumption, and plasma levels of HDL among 325 postmenopausal women who were not receiving hormone-replacement therapy in the Nurses' Health Study. Overall, the mean adjusted HDL level among women who consumed at least 7 g of alcohol per day (approximately half a drink) was 7.8 mg per deciliter (0.2 mmol per liter) higher than the level among women who consumed less than 7 g of alcohol per day (64.1 vs. 56.3 mg per deciliter [1.7 vs. 1.5 mmol per liter], $P<0.001$). The HDL levels
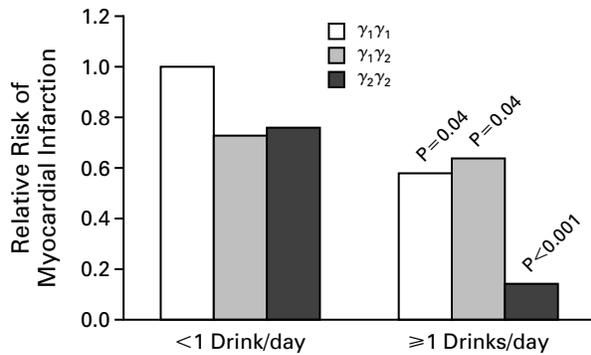
Figure 1. Multivariate Relative Risk of Myocardial Infarction According to the *ADH3* Genotype and the Level of Daily Alcohol Consumption.

In addition to adjustment for the matching factors of age, smoking status, and time since randomization (in six-month intervals), the analyses were adjusted for body-mass index (≤23.01, >23.01 to 24.40, >24.40 to 26.40, or >26.40), frequency of vigorous physical activity (<1, 1 to 4, or ≥5 times per week), presence or absence of a family history of myocardial infarction, presence or absence of random assignment to aspirin use, and presence or absence of a history of hypertension, diabetes, and angina at enrollment. The P values are for the comparison with the values in men who consumed less than one drink per day and who were homozygous for the γ_1 allele (the reference group); the lowest relative risk of myocardial infarction (0.14; 95 percent confidence interval, 0.04 to 0.42) was for the group of men who drank daily and who were homozygous for the γ_2 allele (P=0.02 for the interaction between the genotype and the level of alcohol consumption).

were higher among women who drank at least 7 g of alcohol per day than among those who drank less than 7 g per day in all three genotype groups (Fig. 2B). Similar to the findings in the men, HDL levels among the women who drank at least 7 g of alcohol per day were highest among those who were homozygous for the γ_2 allele, intermediate among the heterozygotes, and lowest among those who were homozygous for the γ_1 allele (P=0.02 for the interaction).

DISCUSSION

We observed a strong interaction between the *ADH3* genotype and the level of alcohol consumption in relation to the HDL level and the risk of myocardial infarction. Since the predominant function of alcohol dehydrogenase type 3 is to metabolize alcohol, this finding is consistent with the hypothesis that a slower rate of clearance of alcohol enhances the beneficial effect of moderate alcohol consumption on the risk of cardiovascular disease.

Approximately half the apparent benefit of alcohol consumption on the risk of myocardial infarction can be explained by an increase in the HDL level.[6,21-23] We found that HDL levels were higher among men who consumed at least one drink per day in all three of the *ADH3* genotype groups, but that the levels were
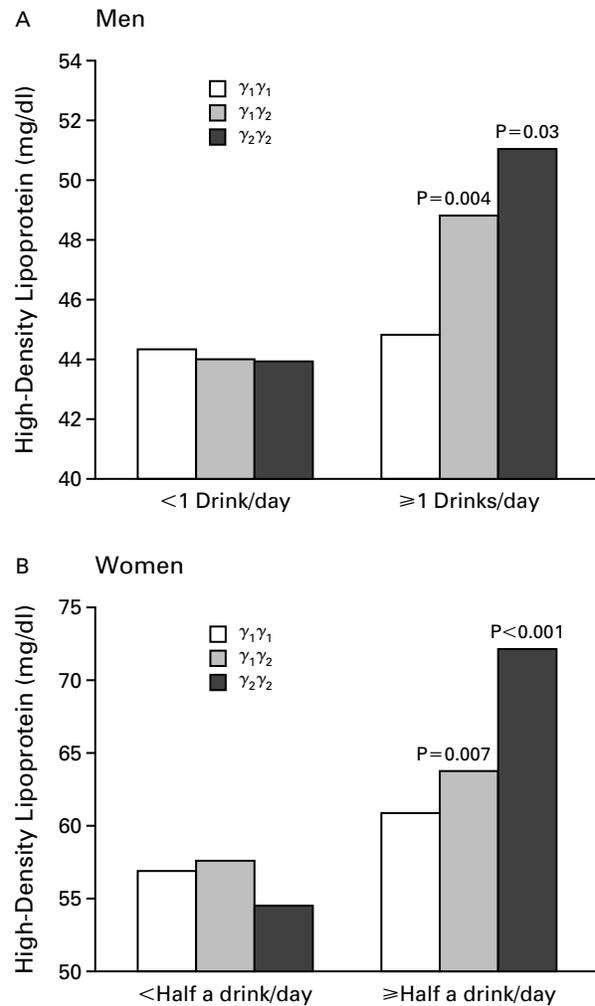
Figure 2. Adjusted High-Density Lipoprotein Levels According to the Level of Alcohol Consumption and the *ADH3* Genotype in 385 Patients with Myocardial Infarction and 385 Controls in the Physicians' Health Study (Panel A) and 325 Postmenopausal Women in the Nurses' Health Study Who Were Not Receiving Hormone-Replacement Therapy (Panel B).

In Panel A, the P values are for the comparison with the values in men who consumed less than one drink per day and who were homozygous for the γ_1 allele (the reference group) (P=0.05 for the interaction). The analysis was adjusted for age (as a continuous variable), smoking status (never smoked, past smoking, or current smoking), body-mass index (≤23.01, >23.01 to 24.40, >24.40 to 26.40, or >26.40), frequency of vigorous physical activity (<1, 1 to 4, ≥5 times per week), presence or absence of a family history of myocardial infarction, presence or absence of random assignment to aspirin use, and presence or absence of a history of hypertension, diabetes, and angina at enrollment. In Panel B, the P values are for the comparison with the values in women who consumed less than 7 g per day of alcohol per day (defined as approximately half a drink) and who were homozygous for the γ_1 allele (the reference group) (P=0.02 for the interaction). The analysis was adjusted for age (<61.5 or ≥61.5 years), body-mass index (<22, 22 to <25, 25 to <29, or ≥29), whether or not blood had been obtained after an overnight fast, whether or not hormone-replacement therapy had been used in the past, and pack-years of smoking (to 1990). To convert values for high-density lipoprotein to millimoles per liter, multiply by 0.02586.

highest among those who were homozygous for the γ_2 allele. Our data suggest that the reduction in the risk of myocardial infarction attributed to the interaction between the *ADH3* genotype and the level of alcohol consumption is not due solely to an increase in the HDL level. However, we cannot accurately estimate how much of the modifying effect of the *ADH3* genotype on myocardial infarction is due to its effect on the HDL level, since there were only five patients who consumed at least one drink per day and who were homozygous for the γ_2 allele.

Some have suggested that the inverse association between moderate alcohol intake and the risk of myocardial infarction does not represent a true causal relation, but rather that alcohol is a surrogate for favorable socioeconomic or lifestyle factors associated with a reduction in risk.[24] It is unlikely that the *ADH3* genotype is associated with these potentially confounding factors, and we observed no such associations in our data. The finding of an effect of the functional *ADH3* polymorphism on the relations between moderate consumption of alcohol and the risk of myocardial infarction (and the HDL level) lends support to the plausibility of a causal interpretation. Associations observed in nonrandomized epidemiologic studies may be attributed to potentially confounding factors. Observed associations between the risk of a disease and the presence of functional variants in genes that lead to the metabolism or transduction of the factor that underlies the disease add substantial support to the idea that the exposure to the factor is directly related to causation.

Similarly, it has been proposed that the protective effect of the consumption of alcoholic beverages on heart disease may be due to constituents of alcoholic beverages other than ethanol (e.g., antioxidants such as flavonoids).[25] The fact that alcohol dehydrogenase type 3 metabolizes ethanol, and not other compounds, suggests that ethanol is responsible for the protective effect. A key problem in environmental epidemiologic studies is that humans are exposed to complex mixtures of compounds, so identifying the specific beneficial or harmful compounds may not be possible. Improving our ability to identify specific lifestyle and environmental factors as causes of a given disease may prove to be one of the main benefits of the study of common variants in metabolic genes and disease.

The prospective design of our study, the relatively large number of newly diagnosed cases, and the high rate of completeness of follow-up data strengthen the validity of our results. Nonetheless, our study has potential limitations. Since alcohol intake was estimated on the basis of the subjects' responses to questionnaires, it may underestimate the true intake. Although the exact relation between self-reported intake and true intake is not known, similar questionnaires have been shown to provide useful estimates of alcohol intake over extended periods.[26] Evidence suggests that the ranking of the intake of alcohol among the subjects from low to high in the Physicians' Health Study is quite accurate. Previous studies of this cohort have shown that the self-reported alcohol intake can be used to predict the risk of myocardial infarction,[3] diabetes,[27] stroke,[28] and death from any cause.[29] Such results are consistent with those of other studies that assessed alcohol intake in much greater detail. The correlation between HDL levels and alcohol intake in our group is consistent with the results of experimental studies of alcohol administration, and it thus supports the validity of the ranking of self-reported alcohol intake in this study population.

Another issue that needs to be addressed is the range of alcohol consumption over which the *ADH3* genotype influences the risk of myocardial infarction. Although we would not expect the *ADH3* genotype to have any effect on the risk of myocardial infarction among those who do not drink alcohol, we observed a nonsignificant reduction in risk among men who consumed little or no alcohol and who were homozygous for the γ_2 allele. In addition, among men who consumed alcohol daily, there was no significant difference in the risk of myocardial infarction between heterozygotes and those who were homozygous for the γ_1 allele despite the observed difference between these groups in HDL levels. This discrepancy could be attributed to the limited statistical power of the study, since confidence intervals in these subgroups were broad. Alternatively, some other mechanism may be at work.

Our study lacks the statistical power to determine the effect of the *ADH3* genotype on those who are heavy drinkers. Thus, our results are only generalizable to populations with light-to-moderate levels of alcohol consumption. Heavy consumption of alcohol is a risk factor for several diseases or conditions, such as alcoholism, stroke, and liver disease. Persons with a slow rate of metabolism of ethanol may have a reduced risk of coronary heart disease; however, they may be at higher risk for other alcohol-associated diseases. Studies among male and female populations with high levels of alcohol consumption are needed to assess this possibility.

In summary, we observed a marked and significant interaction between moderate alcohol consumption and the *ADH3* polymorphism. Men who drank daily and were homozygous for the γ_2 allele had a substantially decreased risk of myocardial infarction — a decrease that was at least partially attributable to an increase in HDL levels.

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