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Alcohol consumption and high-density lipoprotein levels: the effect of *ADH1C* genotype, gender and menopausal status

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Abstract

We previously demonstrated that a functional polymorphism in alcohol dehydrogenase type *1C (ADH1C*, also known as *ADH3)* modifies the association between moderate alcohol consumption and high-density lipoprotein (HDL) levels and risk of myocardial infarction among older men. In this study, we investigated the effect of the *ADH1C* γ_1 and γ_2 alleles on the relationship between alcohol consumption and HDL levels among four populations with varied exposure to endogenous and exogenous estrogens: premenopausal women, middle-to-older aged men, postmenopausal women currently using postmenopausal hormones (PMH) and postmenopausal women not currently using PMH. We observed an interaction between moderate alcohol consumption and *ADH1C* genotype on HDL level that was similar among middle-to-older aged men and postmenopausal women not using PMH. Among the moderate drinkers (approximately a half a drink per day for women and a full drink per day for men), there was a significant 5.3 mg/dL ($P = 0.02$) higher level of multivariate adjusted HDL level comparing the γ_2 homozygotes (slow oxidizers) to the γ_1 homozygotes (fast oxidizers). This interaction was not present among premenopausal women or postmenopausal women using PMH, who had higher overall HDL levels irrespective of alcohol consumption. Our results confirm that *ADH1C* genotype modifies the association between alcohol consumption and HDL levels among men and postmenopausal women not using PMH who drink moderately. However, this was not observed among individuals with estrogen-elevated HDL levels, specifically premenopausal women and postmenopausal women taking PMH, suggesting that these populations may benefit less from alcohol consumption with respect to coronary heart disease.

Keywords: ADH1C; Alcohol; Estrogen; High-density lipoprotein; Genetics; Epidemiology; Alcohol metabolism

1. Introduction

Moderate alcohol consumption, approximately 1 drink per day for women and 2 drinks per day for men, is associated with a reduction in risk of coronary heart disease (CHD) [1–4]. The gender difference in the amount of alcohol consumed to achieve similar cardiovascular benefits is attributed to three factors: body size, amount of body fat and efficiency of alcohol metabolism [5,6]. Genetic differences in alcohol metabolizing genes are a determinant of alcohol metabolic efficiency and may contribute to the susceptibility to alcohol-associated diseases [7]. A polymorphism in alcohol dehydrogenase type 1C *(ADH1C*, also known as

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ADH3) that slows the rate of ethanol oxidation has been associated with a greater inverse association between alcohol consumption and risk of myocardial infarction, and a more positive association with high-density lipoprotein (HDL) levels [8]. In a case–control study of coronary heart disease nested within the prospective Physicians' Health Study cohort, the inverse association of daily alcohol consumption was greatest among those homozygous for the slower oxidizing allele (γ_2) [8]. Furthermore, HDL levels among the daily drinkers were highest for the slow oxidizers. A similar relation with HDL levels was also observed among 325 postmenopausal women not using postmenopausal hormones (PMH) [8].

Premenopausal women have a substantially lower risk of CHD compared to similar-aged men; this is often attributed to the cardiovascular benefits of endogenous estrogens [9]. Both alcohol consumption and estrogens raise HDL levels. Premenopausal women and postmenopausal women who use PMH have higher HDL levels compared to postmenopausal women who do not use PMH [10]. Although alcohol consumption has been shown to raise HDL levels among premenopausal women [11], the effect of alcohol metabolic capacity on HDL levels and CHD risk among individuals who have estrogen-elevated HDL levels has not been elucidated.

In this study, we investigated the effect of the *ADH1C* γ_1 and γ_2 alleles on the relationship between alcohol consumption and HDL levels among different populations with varied exposure to endogenous and exogenous estrogens, specifically middle-to-older aged men, premenopausal women, and postmenopausal women who either use or do not use postmenopausal hormones. These populations were obtained from three distinct cohorts: the Health Professionals' Follow-up Study, the Nurses' Health Study, and the Nurses' Health Study 2.

2. Materials and methods

2.1. Subjects and study design

The Health Professional Follow-up Study (HPFS) is a prospective cohort of 51,529 United States male health professionals (dentists, pharmacists, veterinarians, podiatrists, and osteopathic physicians) who were between the ages of 40 and 75 years when they responded to the baseline questionnaire in 1986. In 1993–1995, a blood sample was requested and collected from 18,225 participants. This cohort and the method for blood collection have been previously described in detail [12]. Among those who returned a blood sample, 8922 men who did not have completed questionnaire information on diet, cigarette smoking, alcohol consumption, and physical activity from 1986 to 1994 were excluded from this analysis. In addition, 208 men with CVD, diabetes, gastric or duodenal ulcer, liver disease, and cancer (except nonmelanoma skin cancer) were excluded. From the remaining men, 468 men were randomly selected according to different patterns of self-reported alcohol consumption determined by frequency, amount, and time (e.g. with meals) of alcohol consumption. The different patterns included abstainers, binge drinkers, moderate drinkers, light drinkers (less than a drink per day) and heavy drinkers (more than 2 drinks per day). The light drinkers and heavy drinkers were also selected according to the proportion of alcohol consumed with meals (<25%, 25–75%, more than 75%). We oversampled the study population across drinking patterns to increase statistical power to test differences in biomarkers at higher levels of alcohol consumption. Alcohol consumption was calculated by summing the frequency and amount of beer, red wine, white wine, and spirits as reported by the participants on the food-frequency questionnaire in 1994. Information on potential confounders was obtained from the 1994 questionnaire or prior questionnaires if the relevant information was not available.

The Nurses' Health Study 2 (NHS2) is a prospective cohort of 116,671 United States registered female nurses who were between the ages of 25 and 42 years when they responded to a baseline questionnaire in 1989. This cohort has been previously described in detail [13]. During 1996–1998, blood samples were obtained from over 29,000 participants. Among those who responded to the questionnaire in the blood collection kit, blood samples were selected from premenopausal women who were not using any hormones and who collected their blood sample during the luteal phase of the menstrual cycle. Participants in this study were selected based on a range of alcohol consumption patterns similar to those described for the HPFS cohort. We excluded women with any of the previously described preexisting conditions. From the remaining women, 453 women were selected from the different categories of self-reported alcohol consumption pattern. Self-reported alcohol consumption, recorded in categories based on drinks per week, was obtained from the questionnaire provided with the blood collection kit. Information on potential confounders was obtained from either the questionnaire at blood draw, or the 1997 questionnaire.

The Nurses' Health Study (NHS) is a prospective cohort of 121,700 female United States registered nurses who were between the ages of 30 and 55 years when they responded to a baseline questionnaire in 1976. In 1989–1990, blood samples were collected from 32,826 of the cohort members [14]. The women included in this study had been initially selected for either a nested case–control study of breast cancer or a nested case–control study of myocardial infarction. The NHS participants in the nested case–control study of breast cancer have been previously described [15]. We assayed HDL levels among 464 breast cancer cases and 466 controls. Among the participants selected for a nested case–control study of myocardial infarction, only the randomly selected controls were included in the present analysis because of the strong relationship between HDL levels and myocardial infarction. Controls were randomly selected