Is the association between alcohol use and coronary artery disease causal? Evidence from a long-term twin study¹

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Many observational epidemiologic studies of the association between alcohol use and the occurrence of coronary artery disease (CAD) have been conducted, with most studies observing the lowest risk of disease among light to moderate drinkers, whereas abstainers and heavy drinkers have higher rates of CAD (1). The lowest risk is seen among those with an average consumption of 33 g/d, which is ~20% lower than among nonusers. This U-shaped association has been robust to adjustment for potential confounders, but the causality of the relation cannot be established by using observational cohort studies alone. It would be ethically and logistically impossible to conduct a randomized clinical trial, so we need to seek other study designs to test the causal nature of the association. One such design is through the identification of genetic variants associated with alcohol use. These Mendelian randomization analyses use the genetic variant as an instrumental variable; a recent such study was conducted in 261,991 individuals with 20,259 CAD events drawn from multiple cohorts. It found that those with the A allele of the genetic variant [rs1229984 variant in the alcohol dehydrogenase 1B gene (ADH1B)] drank less and had lower odds of CAD, with the authors concluding that reduction in alcohol consumption even among light to moderate alcohol users would be beneficial for cardiovascular health (2). Roerecke and Rehm (3) recently reported some limitations of the Mendelian randomization study and called for new designs that move beyond traditional observational studies. One such approach is to use twin and within-family designs. In these designs, unmeasured genetic and within-family shared factors are adjusted for by comparing the disease outcomes of sets of siblings who differed in their alcohol use as adults. Longitudinal family-based cohorts are needed to make this possible.

In the current issue of the Journal, Dai et al. (4) report results from a 41-y follow-up of the National Heart, Lung, and Blood Institute (NHLBI) Twin Study. This prospective study in initially middle-aged men has over the years yielded important insights into genetic influences on cardiovascular disease risk factors and outcomes. The present analysis focused on alcohol use assessed at the first examination of the twins in 1969, when they were 48 y old on average, who were born during 1917–1927 and recruited through the World War II National Academy of Sciences–National Research Council Veteran Twin Registry for more detailed clinical workup. These 843 twins were followed for mortality until 2010; and CAD, cardiovascular, and overall mortality were examined. A standard cohort analysis of the twins as individual men showed that baseline alcohol use was associated with a 6% (95% CI: 1%, 11%) reduced risk of CAD per 10 g alcohol use per day. No association was seen for cardiovascular disease or all-cause mortality, implying that alcohol conferred an increased risk of non-CAD mortality. Similar results were seen for the within-family analyses in which the twin brother difference in alcohol use was analyzed with respect to differences in CAD mortality of the brothers to determine whether the higher-consuming brother had a lower risk of CAD than did the brother who drank less. Because the twin brothers are matched on age, sex, family background, and partially (for dizygotic twins) or fully (for monozygotic twins) for genetic background, this design adjusts for many known and unknown factors affecting CAD risk. In both the standard cohort analysis of individuals and of the within-pair differences, the results were robust to adjustment for known CAD risk factors. In addition, a carefully considered set of sensitivity analyses did not materially change the results.

At first glance, the linear result of decreasing risk with increasing alcohol use seems at odds with the U-shaped association reported in recent such studies. Roerecke and Rehm (1) showed that the twin men in the NHLBI study are overall modest drinkers, with an average consumption at baseline of 8.6 g/d, and 90% drank <30.9 g (the median of the highest fifth of consumption; the authors’ Table 1). With 19 CAD deaths in the highest fifth, very few deaths can have occurred among men with alcohol use amounts greater than the nadir point (33 g/d) shown by Roerecke and Rehm (1). Thus, the study is underpowered to detect a U-shaped association and is informative only about the descending arm of the association from 0 to 33 g. For this, the 6% decrease in CAD mortality per 10 g is consistent with the 20% difference from 0 to 33 g on the basis of the meta-analysis. One might conclude that the twin analysis is supportive of a causal association of increasing alcohol use (up to ~30 g/d) on lower CAD mortality risk.

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Nonetheless, it is in contrast to the study by Holmes et al. (2) of Mendelian randomization results. Thus, the causality of the association remains unresolved and requires both larger and better molecular genetic analyses, and larger twin analyses. Such twin cohorts with data on alcohol use and mortality fortunately exist (5).

The long persistence of the results is of interest, perhaps reflecting the relative stability of alcohol use in adult men over the life span. Although the results may spur further studies into the mechanisms between light to moderate alcohol use and CAD risk, the results of the present analysis should not be used to encourage alcohol use. There was no overall association with mortality for the range of alcohol consumption of these initially middle-aged men, and we know from studies in young twin pairs, in which one twin drinks more than the other in adolescence, that alcohol use is associated with multiple worse outcomes later, both in the United States (6) and Finland (7).

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REFERENCES