Alcohol and the Heart

Does Raising High-Density Lipoprotein Matter?

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The well-documented capacity of alcohol consumption to increase levels of high-density lipoprotein (HDL) cholesterol has generated attempts to assess the extent to which this effect might contribute to the reduced incidence of coronary heart disease (CHD) that has been observed in moderate consumers of alcohol. Several reports based on multiple regression models in observational cohort studies have indicated that this contribution may be substantial. However, Magnus et al., who have performed a similar analysis in a large Norwegian cohort, have concluded that serum HDL cholesterol is not in the causal pathway connecting alcohol to CHD protection. The validity of the data that were used for their analysis is supported by their documentation of dose-dependent relationships of moderate alcohol intake with both higher HDL cholesterol and lower CHD risk.

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This article is important for several reasons. First, there is a well-known publication bias against negative findings, which can result in overestimation of effect magnitude. Second, the study may reveal important heterogeneity in the alcohol-HDL-mortality interactions across populations. The authors point out potentially important differences between their Norwegian population and other European and American populations, not the least of which may be the genetic milieu in which the interactions operate. Third, the disparate results between this and other studies may prompt further investigation of the impact on CHD risk of the effects of alcohol on functional properties of specific HDL populations or pathways influencing HDL metabolism that, as discussed below, may yield a stronger connection with the cardioprotective effects of moderate alcohol consumption than HDL cholesterol does.

Interestingly, although the cohort studied by Magnus et al is substantially larger than that in prior studies, their number of CHD cases (n=1115) is actually comparable to that in the preceding studies (n=979) that credited much of the alcohol effect to HDL cholesterol. Thus, the article does not negate these earlier findings simply on the basis of sample size. It is conceivable, as suggested by the authors, that the limitation of their analyses to fatal CHD may be a factor. If so, this raises the intriguing possibility that the mechanisms underlying the impact of alcohol on this end point may differ from those responsible for the relation of alcohol intake to nonfatal CHD events. In this regard, it would be helpful to know the relationship of HDL cholesterol to both fatal and nonfatal CHD in the study cohort. Another concern suggested by the authors is the potential for confounding by lifestyle practices. This introduces the possibility that measurement errors and departures from linearity could affect the degree to which adjustment successfully corrects for these factors.

Although nonlipoprotein effects of alcohol such as those reported for markers of hemostasis and insulin sensitivity have been proposed to contribute to a benefit of alcohol on CHD, should the analyses by Magnus et al lead to rejection of a role for HDL? Fundamental to addressing this question is the fact that HDL comprises a heterogeneous collection of particles with multiple functional properties. HDL cholesterol, although a strong biomarker for assessing cardiovascular disease risk, represents only one feature of HDL particles, namely their cholesterol content, and there is a growing body of evidence that HDL cholesterol does not always reflect the properties of HDL particles that may be most critical for their cardioprotective functions. For example, the capacity of HDL to promote efflux of cholesterol from macrophages has been shown to be strongly related to measures of atherosclerosis severity independently of HDL cholesterol. Although it remains to be determined whether a specific component of HDL may be primarily responsible for this relationship, it is notable that moderate alcohol intake has been reported to increase macrophage cholesterol efflux in conjunction with greater content of prebeta HDL, a minor species that has a major role in facilitating cellular cholesterol removal. Multiple other effects of alcohol on metabolism of HDL particles and their constituent proteins and lipids could be invoked as contributing to reduced CHD risk in a manner that may not be consistently related to HDL cholesterol in various populations and clinical settings.

Finally, consideration should be given to the possibility, based on clinical trials of a number of therapeutic modalities, that increases in HDL cholesterol may not result in the CHD benefit that would be predicted by extrapolation from prospective observational studies. This again raises the question of the specific features of HDL particles and/or metabolism that may be most important for CHD protection. Moreover, the epidemiological associations of HDL cholesterol with CHD risk may reflect to an important extent the tight interrelations of HDL metabolism and other factors affecting risk, both measured and unmeasured. In the end,
nondrinkers who hope to reduce CVD risk by raising their HDL cholesterol levels should, for a variety of reasons, heed the advice of the American Heart Association\(^{17}\) not to consider alcohol a therapeutic option for CVD risk reduction.

Disclosures

None.

References


Key Words: Editorials | alcohol | atherosclerosis | lipoproteins | lipoproteins, HDL | cardiovascular disease
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Circulation. 2011;124:2283-2284
doi: 10.1161/CIRCULATIONAHA.111.067223
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/124/21/2283

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