

Diet, alcohol, and health: a story of connections, confounders, and cofactors^{1,2}

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“With ruin upon ruin, rout on rout, confusion worse confounded” —John Milton: *Paradise Lost*, II, 1667.

There is wide acceptance that the best evidence for cause-and-effect relations in health studies is provided by randomized, controlled, preferably blinded clinical experiments. However, the conduct of such trials is difficult in some areas. The reasons for this difficulty may include ethical, financial, and practical considerations, all of which apply to the study of the long-term consequences of alcohol consumption. A vast amount of data links heavy drinking to increased risk of various adverse outcomes, and substantial amounts of data link lighter drinking to a lower risk of several outcomes (1–3). Much of the best evidence for these connections comes from prospective, observational epidemiologic studies. By statistical adjustment, these studies attempt to minimize indirect explanations, ie, confounding, with variable success. Probably the major qualitative difference between prospective observational studies and controlled trials is the impossibility of complete control for confounding in the former.

For a spurious association to occur, the potentially confounding variable must be related to both the exposure and the outcome traits under study. This is common. Age and sex are related to so many health traits and outcomes that they are almost invariably controlled for in epidemiologic studies or, alternatively, sex-specific data are presented. With respect to alcohol and health outcomes, the strong association between alcohol drinking and smoking is often important because smoking has important relations to many medical conditions. Without control for associated smoking, some of the apparent adverse effects of heavy drinking might really be due to tobacco. It is likely that lack of control for smoking was substantially responsible for failure to uncover sooner the inverse relation between alcohol and coronary heart disease (CHD) (2). Without such control, the positive smoking-CHD association readily masks the lower CHD risk of light drinkers.

Dietary habits are also important potential confounders of alcohol-health relations. The association between food habits and alcohol intake may go both ways, with each influencing the other (4). Because sociocultural factors play a large role in determining dietary habits, generalization is sometimes questionable. The article by Kesse et al (5) in this issue of the Journal addresses this issue in a large population of female French teachers. Not surprisingly, wine was the preponderant alcoholic beverage choice. The data confirm the drinking-smoking relation, with smoking prevalence being 4 times as great in heavy drinkers (those who consumed ≥ 32 g ethanol/d) compared with non-

drinkers. Heavy drinkers also had generally less healthy dietary habits. The authors suggested that some proportion of adverse health outcomes associated with heavier drinking might be due to less favorable eating patterns. In contrast, the lighter drinkers did not have healthier dietary habits than did nondrinkers. Thus, they concluded that the lower mortality of lighter drinkers than nondrinkers was likely not due to confounding by dietary habits. This study did not address confounding related to alcoholic beverage choice, previously discussed in this journal (6, 7).

In the early 20th century, confounding by dietary habits was widely accepted as explaining several obvious connections between heavy drinking and organ damage. This was clearly modulated by the description of classic vitamin deficiency diseases and the observation that, in developed countries, these conditions occurred mostly in alcoholics. Thus, nutritional deficiency was believed to be the probable basis of alcoholic cirrhosis until liver toxicity by alcohol was unequivocally shown (1). Because not all chronic heavy drinkers develop cirrhosis, it is presumed that cofactors or susceptibility traits are also involved. Recognition of thiamine deficiency or beri-beri resulted in a diversion in thinking about alcoholic cardiomyopathy (2). In the 19th century, many observers noted heart damage in some very heavy drinkers. Later, the fact that beri-beri syndrome can include heart failure resulted in the hypothesis that chronic beri-beri could cause an enlarged, weakened heart. However, the pathophysiology of beri-beri and that of alcoholic cardiomyopathy differ greatly, and the current belief is that chronic heavy alcohol use can be cardiotoxic (2). Historical episodes also suggest that small amounts of arsenic or cobalt are synergistic with heavy alcohol intake in the production of heart muscle damage; ie, they interact as cofactors (2). Cofactors for both alcoholic cirrhosis and cardiomyopathy may include genetic susceptibility, viral infections, and nutritional factors.

Kesse et al properly cite folate intake and alcohol as an example of a dietary interaction in relation to breast or colon cancer risk. The breast cancer connection has great interest because data relating alcohol to increased risk are more consistent for breast cancer than for bowel cancer and may involve light-to-moderate as well as

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heavy alcohol intake (8). Yet, in the Nurses' Health Study, those in the highest quintile of folate intake (≥ 400 $\mu\text{g}/\text{d}$) showed no increased risk associated with increasing alcohol intake (9). Note that most persons with high folate intake took dietary supplements.

In this age of molecular genetics, it seems possible to circumvent some of the confounding inherent in observational data. An elegant example is a recent study of outcomes related to genetic pleomorphism for an enzyme involved in regulating alcohol metabolism (10). Persons with the *ADH3* allele ("slow metabolizers") had 1) higher blood alcohol concentrations for a longer period of time, 2) higher HDL concentrations, and 3) lower CHD risk than did "fast metabolizers." Fast or slow alcohol metabolism was unrelated to lifestyle traits, indicating that confounding by these was unlikely. This study points out the path of much probable future research.

We are in an era of sophistication and skepticism about relations or connections. We require well-controlled data to convince us of probable causality. With respect to dietary habits and alcohol drinking, the changing nature of personal habits and the lack of precise measurement instruments are special limitations. We are beginning to deal more effectively with possible dietary confounders of the consequences of heavy drinking, light drinking, and beverage choice. We are comfortable with the concept that an association may simultaneously be, in part, causal, confounded, and connected to cofactors. Now that we understand confounding better, we might disagree with the poet's expression that confounding is worse than confusion. We must deal with the latter and avoid the former. 🌱

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