

Our results from patients with acute dyspnea indicate that biomarkers of lymphatic growth could be used to identify subjects with HF from other causes of dyspnea, and potentially enhance rapid diagnostic accuracy in addition to natriuretic peptides. The prospective results from the MDC-CC study cohort indicate that VEGF-D could also be an early predictor of future HF, which could represent early adaptation to increasing demands of the lymphatic system. Besides the role of VEGF-D in the lymphatic system, it is also possible that VEGF-D could be linked to HF through other mechanisms, such as coronary atherosclerosis, cardiac remodeling, or pulmonary vascular remodeling. An experimental *in vitro* study demonstrated that VEGF-D serves as a stimulator of myofibroblast growth and collagen synthesis (5), and it could also be hypothesized that raised VEGF-D may reflect an adaptation to increased cardiac strain in the subclinical phase of HF. This view is supported by the significant correlations between VEGF-D and NT-proBNP. The results need to be replicated in further studies, for both men and women. However, we conclude that high VEGF-D appears to be a new biomarker of pulmonary congestion and HF in both dyspnea patients and the general population.

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## Alcohol

### Cardiovascular Disease and Cancer



*Complete abstinence is easier than perfect moderation.*

—St. Augustine

The paper concluding “light and moderate alcohol intake might have a protective effect on all-cause and CVD-specific mortality” (1) and the unbalanced accompanying editorial (2) deserve comments. First, this new post hoc analysis from the National Health Interview Surveys should be considered hypothesis-generating at best. However, the sophistication of the multivariable adjustments contrasted with a 9% attrition rate and a limited reliability of data: first, self-report for hypertension and even alcohol use; and second, arbitrary and limited number of categories for confounding variables thus potentially generating residual confounding (e.g., education level or smoking status); and third, no sensitivity analysis to assess how robust the association is to potential unmeasured/uncontrolled confounding (3). Accordingly, the validity, reliability, and generalizability of the findings deserve scrutiny.

Second, the term “moderate alcohol use” is usual but should be avoided in medical literature. Public health advocates use the term “drinking at low risk.” In the United Kingdom, as in France, the Chief Medical Officer warns both men and women to keep health risks from alcohol to a low level: “it is safest not to drink more than 14 units a week on a regular basis.” Moreover, in this U.S. study 1 alcoholic drink-equivalent contains 14 g of alcohol (1), but it is 8 and 10 in the UK and in France, respectively. Self-reporting is also challenging as the result depends on the size of the glass and the strength (i.e., usually 125 to 175 ml and 11° to 14° for wine). “Moderate alcohol use” is a marketing tool of the industry to promote sales as shown by the flawed French and UK Responsibility Deal (4). The one-third of Health eHeart participants

who believed alcohol to be heart healthy drank substantially more alcohol than the others and cited the lay press as the origin of that perception (5).

Third, alcohol is classified as a human carcinogen (class 1) by the International Agency for Research on Cancer, with a dose-related increase in prevalence of several cancers either exponentially (e.g., oral cavity and pharyngeal cancers) or linearly (e.g., esophageal and breast cancer), beginning at the level of the first to second drink per day.

Fourth, in the study by Zhao et al. (1), the representation of their reference 27, ignored by de Gaetano and Costanzo (2) contrasted with the authors' conclusion (see ref. 27 in Zhao et al. [1]). This Mendelian randomization based on individual participant data suggests that "reduction of alcohol consumption, even for light to moderate drinkers, is beneficial for cardiovascular health."

Advertising for alcohol has skyrocketed and the increase in alcohol use, not only high-risk drinking, in the United States constitute a public health crisis.

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## REPLY: Alcohol

Cardiovascular Disease and Cancer



We appreciate the comments from Dr. Braillon on our recent publication (1). We have responded to the comments as listed sequentially in the letter. First, the self-reported responses used to define variables

and residual confounding are study limitations and are described in the Discussion. Additionally, we conducted stratified analyses by diagnosis of hypertension and found similar results in both strata. Sensitivity analyses by smoking status revealed that protective effect was more pronounced in never- or ever-smokers. Second, we are aware of the different glass sizes, strengths, alcohol types, and recommended units per week in different countries, and we are working to address these issues in our next studies. Our study was not sponsored by alcohol-related industry, thus, we cannot comment on the use of "moderate alcohol use" as a marketing tool by industry. We intend to use the nomenclature similar to earlier studies that allows for comparison. Third, we agree with the author that drinking 1 to 2 drinks per day is hazardous, which is similar to our study conclusion. Fourth, we agree that our conclusion is not in line with the Mendelian randomization study (2), and we discussed this in our publication. We should keep in mind that the Mendelian randomization study is not the "gold standard" with which to make causal relationship conclusions (3).

We conclude that a J-shaped association exists between alcohol consumption and risk of mortality. Although we used nationally representative samples and robust statistical methods in our study to address previous studies' limitations, a significant amount of work is needed to address different types of alcohol use, recall bias, and nomenclature that can translated to public health practice. Overall, we re-emphasize that it is too early to conclude that there is a causal protective relationship between light to moderate alcohol drinking and risk of mortality.

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