

Is it the alcohol or polyphenols in red wine that decreases cardiovascular disease?

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Observational epidemiologic studies relating wine and alcohol to health all suffer from the fact that they, of necessity, compare people who prefer certain beverages, but not the beverages themselves. While there have been many intervention trials in animals, randomized trials in humans are less common. Randomized crossover trials, in which each subject receives all interventions in sequence, can be especially important as they tend to avoid baseline differences among subjects and can detect effects of different interventions with smaller numbers of subjects.

This study by Chiva-Blanch G et al, just published in the [American Journal of Clinical Nutrition](#), included 67 male volunteers in Spain who were considered to be at "high-risk" of cardiovascular disease on the basis of increased BMI, smoking, diabetes, hypertension, or other risk factors. About one half of the individuals were taking [ACE inhibitors](#), statins, aspirin, and/or oral hypoglycemic drugs, so the results of this study may be especially relevant for patients in the real world.

The subjects agreed to not consume any alcohol for a baseline period, then for three one-month periods consumed 30 g/day of alcohol as [red wine](#) or as gin, or an equivalent amount of phenolics from dealcoholized red wine. The polyphenol contents of the RW and the DRW interventions were the same. A very high degree of compliance of the subjects with the assigned interventions is evidenced by results of counting numbers of empty bottles of the intervention beverage returned, dietary records, urinary [metabolites](#), etc. Further, there is good

evidence that there were no important changes between periods in diet or [exercise habits](#). The effects of each intervention on a large number of adhesion molecules and chemokines that affect inflammation and relate to the development of vascular disease were evaluated.

The key results of the study were that both ethanol and nonalcoholic compounds in red wine have potentially protective effects that may reduce the risk of vascular disease. Specifically, the authors conclude that "the phenolic content of red wine may modulate leukocyte adhesion molecules, whereas both ethanol and polyphenols of red wine may modulate soluble inflammatory mediators in patients at high [risk of cardiovascular disease](#)."

Specific comments on the study: Most reviewers considered this to be a well-done, comprehensive study. As one reviewer commented: "This is an excellent paper. The results strongly indicate an effect of wine polyphenols on inflammation (in broad and modern terms) and this is just what we expect from the biochemistry and nutritional effects of fruits and vegetables. The effect of ethanol, on the other hand, likely fits a hormetic mechanism, where low doses regularly supplied are protective while high doses in a single shot are worsening the progression of disease." Another reviewer added: "We need more information on separating the effects of beer, wine, and various types of spirits. Some spirits like brandy and whisky can have useful antioxidant effects, so distinguishing effects among different types of beverages may be informative."

Another Forum reviewer commented: "This is a very interesting paper that goes a way towards answering the question whether it is the alcohol or polyphenols in red wine that confer the health benefits. The trial was well conducted and controlled, with very detailed analyses. It would have been interesting to analyse any changes in conventional risk factors after the interventions. It would also have been interesting in the study to

determine the effects on vascular function by, for example, brachial artery activity (flow mediated dilatation)."

Given that the effects of both alcohol and polyphenols on physiologic factors (e.g., platelet function, fibrinolysis) are transient, generally lasting for no more than 24 hours, it was appropriate that the subjects in this study were instructed to consume the intervention substance (RW, gin, DRW) on a daily basis. When drinking is moderate, there is no evidence that having "alcohol-free days" is beneficial to health. Indeed, most epidemiologic studies show better health effects from daily consumption rather than from drinking on a few days per week.

Concerns about the present study: One Forum reviewer stated: "This appears to be a carefully designed and well executed study, but I have four concerns: (1) The study has been undertaken in high-risk individuals, more than half of whom are hypertensive, a quarter dyslipidaemic, and a quarter diabetic. It is not described what happened to the conventional [risk factors](#) during the interventions. (For example, any improvement in inflammatory markers may have come at the cost of higher blood pressure with the alcohol interventions.) (2) Was there any weight change that could have confounded any of the outcomes? (3) Both polyphenol and alcohol biomarkers were measured – did the change in these biomarkers correlate with the changes in any of the inflammatory markers; i.e., any suggestion of a dose response relationship? (4) Even though at least 30 outcome variables were assessed, the authors do not describe any correction for multiple comparisons."

Another Forum reviewer: "This is a well conducted study, and adds to our understanding of the potential cardiovascular benefits of alcohol and the non-alcoholic compounds of alcoholic beverages. However, in this study more than one-half of the high-risk subjects consumed drugs with known anti-inflammatory effects, which could be a confounding factor.

The anti-inflammatory effects of these pharmaceuticals may be responsible for the beneficial results, and may not be related to the RW, DRW and gin interventions." However, others think that this concern is unlikely to be important since this was a crossover study, and there were no changes in lifestyle or medication use between the intervention periods.

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More information: Chiva-Blanch G, Urpi-Sarda M, Llorach R, Rotches-Ribalta M, Guillèn M, Casas R, Arranz S, Valderas-Martinez P, Portoles O, Corella D, Tinahones F, Lamuela-Raventos RM, Andres-Lacueva C, Estruch R. Differential effects of polyphenols and alcohol of red wine on the expression of adhesion molecules and inflammatory cytokines related to atherosclerosis: a randomized clinical trial. *Am J Clin Nutr* 2012. [doi: 10.3945/ajcn.111.022889](https://doi.org/10.3945/ajcn.111.022889)

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