

Moderate Alcohol Use and Reduced Mortality Risk: Systematic Error in Prospective Studies and New Hypotheses

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We have provided recent evidence suggesting that a systematic error may be operating in prospective epidemiological mortality studies that have reported “light” or “moderate” regular use of alcohol to be “protective” against coronary heart disease. Using meta-analysis as a research tool, a hypothesis first suggested by Shaper and colleagues was tested. Shaper et al suggested that people decrease their alcohol consumption as they age and become ill or frail or increase use of medications, some people abstaining from alcohol altogether. If these people are included in the abstainer category in prospective studies, it is reasoned that it is not the absence of alcohol elevating their risk for coronary heart disease (CHD) but, rather, their ill health. Our meta-analytic results indicate that the few studies without this error (i.e., those that did not contaminate the abstainer category with occasional or former drinkers) show abstainers and “light” or “moderate” drinkers to be at equal risk for all-cause and CHD mortality. We explore the history of this hypothesis, examine challenges to our meta-analysis, and discuss options for future research.
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INTRODUCTION

The objectives of our paper consist of, first, providing a brief summary of the history of research efforts surrounding a hypothesis originally articulated by Shaper, Wannamethee, and Walker in 1988 (1), who hypothesized that a systematic misclassification error was present in most prospective studies assessing associations between alcohol use and coronary heart disease (CHD). This history laid the groundwork for testing the hypothesis using a meta-analysis of prospective studies that reported the associations between alcohol use and mortality risk from all causes and CHD (2). Second, challenges to the findings from this meta-analysis are evaluated. Third, options for future research are discussed.

BRIEF HISTORY OF THE SHAPER, WANNAMETHEE, AND WALKER HYPOTHESIS

Shaper and colleagues suggested that the error of including persons terminating or decreasing their alcohol consumption to very occasional drinking in the abstainer category biased the findings toward making drinkers appear to be less vulnerable to CHD and abstainers more vulnerable in prospective studies. As people age and become ill or frail or increase use of medications, their alcohol consumption decreases, some abstaining altogether. If these people are included in the abstainer category, then it is not the absence

Selected Abbreviations and Acronyms

CHD = coronary heart disease
HDL = high-density lipoprotein
RCT = randomized clinical trial

of alcohol that is elevating their risk for CHD but, rather, their compromised health.

Although meta-analyses appraising alcohol use and CHD morbidity and/or mortality have been performed in the past (3–8), our meta-analysis (2) is the second to explicitly address the hypothesis (the first meta-analysis [7] utilized inclusion criteria for studies without error and differed radically from our own). Fifty-four prospective studies evaluating alcohol's association with all-cause mortality (35 prospective studies evaluating CHD mortality) were included. A systematic misclassification error was committed by including as "abstainers" many people who had reduced or stopped drinking, a phenomenon associated with aging and ill health. The studies judged to be error free found no significant all-cause or cardiac protection, suggesting that the cardiac protection afforded by alcohol may have been overestimated. Our results do not prove the error but suggest that the protective effect of alcohol for CHD may have been exaggerated in most epidemiological studies to date and the analysis may reopen the debate in this domain.

The history of the Shaper et al hypothesis stretches back for a quarter of a century. In 1981, two prospective studies (9, 10) suggested that "moderate" drinking was associated with the reduction of incidence of CHD. These two publications drew considerable scientific and public attention, although earlier studies had reported similar findings. Many prospective and case-control studies followed, confirming what became known as the "protective effect." Biological studies demonstrated plausible mechanisms whereby "moderate" doses of alcohol will affect the clotting processes, will increase the protective fraction of cholesterol (high-density lipoprotein [HDL] cholesterol), and may increase elasticity of blood vessels (e.g., 11, 12) in contrast to the positive linear association with heavier alcohol use and blood pressure. However, none of the studies assessing plausible biological mechanisms tell us whether alcohol necessarily is beneficial, even if possible. This directs scientific attention to the importance of strong evidence from epidemiological studies to positively determine if the lower risk of "light" to "moderate" drinkers is actually caused by the theoretical benefits derived from laboratory research versus the possibility that the lower risk is caused primarily by confounding variables or error. It should also direct researchers to more precisely measure levels and patterns of consumption consistent with different proposed biological mechanisms.

There have been at least two major critiques of the epidemiological studies contributing to the protective effect finding. First, considerable evidence suggests that healthy behaviors tend to cluster in the group of "protected" drinkers (11, 13–18) and no amount of statistical controls in prospective studies can eliminate it. We acknowledge this problem but do not pursue it herein.

Second is the Shaper et al hypothesis. The hypothesis was taken seriously in the relevant epidemiological community. Some analysts strove to correct for the error. A deductive meta-analysis (7) utilized seven studies to suggest that the hypothesis had been eliminated. All but one was with the abstainer misclassification error according to our definition of it. By 1996, it could be claimed that the hypothesis had been eliminated (16), citing five prospective studies and one case-control study. Each of these prospective studies contains one or both of the abstainer errors that we evaluate in our meta-analysis. In light of this history, it appeared to us that conclusions from both of these publications did not utilize the rigor we would eventually employ in our efforts to define the abstainer error.

Although the Shaper et al hypothesis was seemingly laid to rest by the mid-1990s, the medical epidemiological literature had all but ignored two major scientific literatures existing somewhat outside its domain, both pertinent to it.

The first supports the Shaper et al hypothesis. Numerous cross-sectional and longitudinal studies (some of the latter with multiple measurement points and in populations characterized with greater longevity) attest that as people progress into late middle and old age, their consumption of alcohol declines in tandem with ill health, frailty, dementia, and/or use of medications (19–33). Longitudinal studies (including those with more than two measurements) found that many people shift over time between complete abstinence and occasional drinking (34–36), alcohol use declines with advancing age (evidence even from the medical epidemiological literature itself [37]), and the alleged protective effect of alcohol is reduced when accounting for variation in drinking patterns over time (38).

The second consists of efforts made in alcohol-related science reflecting more than 50 years of struggle to accurately describe the complex and sometimes elusive patterns of drinking, including variations in these patterns over time (39, 40). These efforts emanated from knowledge that drinking patterns vary across and within populations and that, in any one individual, drinking patterns may be complex, fluctuating over the life course. In addition, it was early understood that specific types of drinking patterns are closely related to specific disease outcomes. Although some recent studies in the medical epidemiological literature have

sought to incorporate variations in drinking patterns over time into their studies (41),* most deal with absolute volume of drinking and some are highly limited in measurement (e.g., measuring drinking solely with respect to its frequency or its quantity per occasion or limiting the time frame of assessment to several days or weeks), thereby containing extremely imprecise measurement and possibly masking potential error. The cause of this, in part, is owed to the fact that many of these studies were not originally or specifically designed to investigate the issue at hand. Hence the alcohol-related findings were published as an afterthought, containing not only imprecise measurement of a difficult-to-measure behavior but also insufficient information on probable confounders (42).

It is in these contexts that our research team felt it worthwhile to evaluate the hypothesis of Shaper et al in a cross-study approach because (a) it had not been adequately tested; (b) other literatures, often ignored by medical epidemiologists, supported that hypothesis; and (c) the great majority of medical epidemiological studies had not integrated a body of knowledge pointing to the necessity of utilizing crisp operational definitions and measurement instruments that would accurately reflect the changing nature of drinking patterns over time among individual respondents.

ARGUMENTS CHALLENGING OUR META-ANALYSIS FINDINGS

We turn attention to what we perceive to be arguments challenging our analyses.

Classification of the Relevant Studies

Two errors were evaluated: the inclusion of former drinkers and occasional drinkers in the abstainer category. Studies without either error did not show abstainers to be at higher risk of all-cause mortality (n = 7 studies) and CHD mortality (n = 2 studies) mortality than were “light” or “moderate” drinkers. Studies with both errors (26 [all-cause mortality studies]; 25 [CHD mortality studies]) showed what had been repeatedly reported in this literature: a J-shape for all-cause mortality and a negative linear shape for CHD. Studies with only the former drinker misclassification error (21 [all-cause mortality studies] and 8 [CHD mortality studies]) showed a J-shape for all-cause mortality and a nonsignificant negative linear association for CHD mortality. Where evaluated, former drinkers in studies only partially or fully without error tended to be at higher

mortality risk than long-term abstainers. Occasional drinkers appeared to be more like “light” drinkers, something for which there is no plausible biological mechanism.

Our operational definitions were rigorous in an effort to isolate studies that were error-free. Inattention to designating or excluding former drinkers clearly indicated error (Table 1 [43–56]). Some studies discriminated former drinkers and occasional drinkers from long-term abstainers in their questionnaires but combined these groups with abstainers in their models. Other analysts made efforts to designate former or occasional drinkers as separate groups or exclude them altogether from their models. However, because of question wording or sequence, former drinkers were judged to have only been partially dealt with in such studies. For example, a difficult study to categorize, illustrating the difficulties and ambiguities in measurement of drinking behavior, was performed by Klatsky (16). Although considerable effort was made to achieve a “pure” abstainer category, abstainers were defined, in part, as never or almost never drinking. “Almost never” was regarded by our research team as highly subjective, suggesting that very infrequent drinkers might have been included in the abstainer group.

The studies were coded to the presence or absence of these errors by two of the investigators. When there was disagreement in coding, the entire research team evaluated the studies and consensus was reached. Additionally, studies in question were assigned to independent analyses. The cases

TABLE 1. Examples of factors alerting us to potential abstainer error

Factors alerting us to error	Probable error
Inattention to classify or exclude former drinkers	Former drinkers misclassified (e.g., 9, 12, 43–51)
Abstainers were coded to include “lifetime abstainers, occasional drinkers, former drinkers and possibly men not admitting to drinking alcohol”	Infrequent and former drinkers misclassified (e.g., 52)
Limited time frame for assessing abstinence (e.g. 24- to 48-hour recall, 3-day recall, 1-week recall, 1-month recall, number of drinks in last 3 days, number of drinks in last month)	Infrequent and former drinkers misclassified (e.g., 10, 53)
Daily drinking assessment (e.g., daily drinking in a week or number of drinks a day or daily drinking)	Infrequent and former drinkers misclassified (e.g., 54)
Use of terms “almost never drink” or “rarely/never drink” or “never or less than once a month”	Infrequent and former drinkers misclassified (e.g., 12, 55, 56)
Former drinkers assigned a category that resulted only from men who volunteered the information	Former drinkers misclassified (e.g., 45)

*However, in this particular case the baseline data consisted of a food frequency questionnaire, and the categorization of drinking committed the error of including occasional drinkers with abstainers.

in which this occurred, more often than not, were those that made an effort to be error free but, because of the questionnaire content, most probably did not completely exclude either former drinkers and/or occasional drinkers from the abstainer category.

Only 7 studies for all-cause and 2 studies for CHD mortality were judged error free. Despite these small numbers, the fact that the analysis was solely hypothesis driven attests to the strong possibility that the nonsignificance of findings among the reduced number of error-free studies was due to the absence of error, rather than to random data dredging.

Use of General Population Studies, Including Younger Adults

Our published study reported results from all studies utilized, regardless of age of measurement. It should be understood that the studies in this research domain have more differences than similarities (as seen in Table A2 of our published paper [2]). In fact, these dissimilarities have often been utilized as an argument to advance the notion that consensus in study results has been found despite cross-study differences.

Studies ranged in ages of measurement. Because the protective effect is thought to operate among middle-aged and older adults, we controlled for respondents' ages in the represented studies, among other pertinent variables. Additionally, we conducted separate analyses of those studies with samples of respondents 35 years of age and older at initial measurement point. The latter did not yield different results compared with the larger sample of studies.

Competing Hypotheses

An argument might be advanced that a number of valid competing hypotheses could eliminate our finding, given that error was operating in the majority of these studies. It took us, literally, a number of years to collect data from the analysts who had performed the studies because quite often these data were simply not reported.* We tested for multiple variables. In some cases, these variables altered the curves in the various strata designating error or lack of it, but our hypothesis was robust to these tests.

Noteworthy is that all meta-analyses to date (our own included) find heterogeneity in cross-study results. Although our testing of competing hypotheses sometimes reduced the amount of heterogeneity, it was not eliminated. Utilizing good hypotheses, some analysts (5, 57)—ourselves included—have gone to extraordinary lengths to reduce

cross-study heterogeneity but without complete success. This suggests to us that there are other errors or confounding in these studies that should be explored and that new hypotheses are warranted.

WHERE DO WE GO FROM HERE?

Our analyses have a number of weaknesses. However, we believe the major weakness is reflected in the nature of the studies themselves, primarily the dominance of inadequate and imprecise measurement of the major explanatory variable. Quite obviously, better study designs with well-articulated questions describing drinking patterns over long periods are in order. As well, the morbidity and case-control literatures in this domain require careful scrutiny for measurement error, and attention should be paid to other disease entities that have reported abstainers to be at higher risk than drinkers.

Still other issues should be addressed. Klatsky (58) states that "...the approximately 10% lower total mortality risk is not large enough to completely preclude the possibility of indirect explanation." He suggests that potential genetic or environmental traits, yet unknown, may operate to account for the increased risk among nondrinkers. We are in agreement that there may be other explanations for the increased risk of abstainers, including the methodological issues we have addressed in our published paper as well as serious problems of confounding. It should not be forgotten that epidemiology deals with crude approximations, beset by confounding—often unmeasured—especially when single estimates or limited measurements are used.

The observation that most of the protection afforded by alcohol operates almost solely for CHD, compared with other diseases, is a critical issue in alcohol epidemiology that should be systematically addressed.† It may be stated in the form of questions: Why is it that statistically significant J-shape associations are obtained for some diseases, whereas significant linear positive associations are found for others? Is this due solely to disease specificity (i.e., the expected nature of the disease in association with alcohol use) or is it due to measurement error or confounding? Most scientific exercises opt for the first explanation, and, in the tradition of medicine, the juncture of epidemiological observation (attempting to best resolve confounding and error) and laboratory affirmation of plausible mechanisms for a given disease is where the story ends. We posit a competing hypothesis—explicated in

*In several cases, the analysts were deceased or had left the field and no longer had the data set in their possession. In two cases, the analysts refused to answer our questions.

†Noteworthy is that alcohol has also been reported to be "protective" for other conditions (e.g., cognitive function, ischemic stroke, and even some cancers).

TABLE 2. Illustrations of a competing hypothesis: Logic and preliminary evidence

The hypothesis: The difference in shape of associations of alcohol with different disease outcomes is a function of measurement error mediated through study design. The hypothesis is based on the following:

1. *J-shaped associations are more often observed for alcohol-related outcomes in diseases dominated by prospective studies, whereas positive linear associations are more often observed for outcomes dominated by case-control studies.* Utilizing a meta-analysis of multiple disease outcomes (59), Table 2 and Figs 1 and 2 illustrate that significant linear associations are typically found for diseases dominated by case-control designs, whereas J-shaped associations are typically found for diseases dominated by prospective study designs.
2. *Prospective studies evaluating alcohol-related disease outcomes are more likely to contain the abstainer error than case-control studies. Abstainer error is less likely to occur in case control studies because greater attention is paid to accurate assessment of exposure, that is, greater attention is paid to past exposure and the duration of exposure, particularly for disease outcomes taking many years to develop.* Corrao et al. (59) reported characteristics of the studies for a number of disease outcomes utilized in their meta-analysis. The clear majority (67%) of case-control studies assessed drinking before diagnosis or assessed lifetime consumption. The clear majority (68%) of prospective studies assessed current consumption (as opposed to consumption in the past or all consumption during follow-up). Assuming that the systematic abstainer error is valid, these cross-design differences suggest that it is more likely to be operating in prospective than in case-control studies (i.e., because case-control studies are more attentive to duration of exposure, they tend to self-correct for this error). (It is noteworthy that Corrao, Bagnardi, Zambon, and Arico (57) found design effects [case-control vs. prospective study] in their meta-analysis for some disease outcomes but did not interpret them via the mechanism of abstainer error.)

The hypothesis has promise because it is supported in at least two additional domains. First, our preliminary observations in a sample of prospective studies evaluating both forms of cancer risk and CHD risk in the same study suggest that when abstainers are found to be at higher CHD risk compared with varieties of drinkers, J-shaped or negative linear curves are also likely to be found for some forms of cancer (e.g., Boffetta and Garfinkel [54] for all cancers combined; Semenciw et al [61] for prostate cancer and all cancers combined; Goldberg et al [60] for all cancers combined; Thun et al [51] for all other cancers, excluding alcohol-related cancers and colorectal cancer, among men and colorectal cancer and all other cancers, excluding alcohol-related cancers, among women; Doll et al [45] for other cancers, excluding lung and large bowel). Second, another meta-analysis supports the proposition. The meta-analysis of alcohol and breast cancer by Ellison et al in 2001 (61) finds increased risk at 12 g of alcohol per day for hospital-based case-control studies (compared with cohort/prospective studies and community case-control samples). Two large cohort studies were analyzed independently in this study for breast cancer mortality. Both find a J-shape curve in contrast to the linear associations found by the entire pool of studies dominated by case-control design studies.

Should this hypothesis be supported, resolution of the abstainer error (most likely to occur in prospective study designs) should bring the conflicting findings from the two designs and from multiple disease outcomes into agreement.

Table 2—one that may resolve some of the contradictions in the alcohol-related epidemiological literature: The difference in shape of associations of alcohol with different disease outcomes is a function of measurement error mediated through study design (see Tables 2 and 3; Figs. 1 and 2).

A further note regarding design is warranted. It has sometimes been suggested that the epidemiological association between alcohol use and CHD can best be resolved through randomized clinical trial (RCT)—certainly the alcohol effect may be more precisely ascertained, particularly in exploring whether low alcohol intake actually conveys a health benefit. RCTs are, of course, the “gold” standard of medical and clinical research and, indeed, may be an asset to the literature regarding alcohol and CHD incidence should the period of measurement be long term and the sample sufficiently large to properly assess both morbidity and mortality. But use of this design faces serious ethical, human subject, logistic, and design obstacles and challenges, and, consequently, any findings may be limited. Additionally, observational and RCTs have been found to differ, with nonrandomized studies showing larger effects than RCTs in some cases (56). Furthermore, results from RCTs would probably not change recommendations currently in existence for the general population. The considerable scientific effort and the massive financial

resources devoted to initiating an RCT may not be warranted in view of the need to better explore “healthier” alternatives to cardiac protection. In any event, any RCT should be performed free of any vested commercial interests.

DISCUSSION

The often used term “moderate drinking” may be inappropriate for at least two reasons. First, its meaning varies across culture and time. Second, the operational definitions of “moderate” drinking vary enormously (62) Such imprecision should be unacceptable to the scientific community. It has been suggested that a more useful term may be “nonharmful”* drinking and that some effort be made to precisely qualify the boundaries of potentially beneficial use (written communication with A. G. Shaper, April 2006).

History attests to exaggeration of both the beneficial and the adverse effects of the use of alcohol (63, 64). In the context of the wide variation of the perceptions and

*Some have suggested “low-risk drinking” as an alternative term (46), although one author of this paper finds it to be inappropriate due to the loaded nature of the term “risk.”

TABLE 3. Proportion case-control studies and prospective studies in a meta-analysis by 12 disease types: Significant associations finding a positive linear association versus a J-shape association

	Total No. of studies	Proportion case-control studies	Proportion prospective designs
Positive linear association with alcohol			
<i>Neoplastic conditions</i>			
Larynx	20	100	0
Esophagus	14	96	4
Oral cavity and pharynx	15	93	7
Breast	29	82	18
Liver	10	80	20
Colon	16	75	25
Rectum	6	66	34
<i>Nonneoplastic conditions</i>			
Chronic pancreatitis	2	100	0
Hemorrhagic stroke*	9	66	34
Cirrhosis of the liver	9	66	34
J-shaped association with alcohol			
Ischemic stroke*	6	50	50
Coronary heart disease	28		100

Adapted from Corrao G, Bagnardi V, Zambon A, La Vecchia C. A meta-analysis of alcohol consumption and the risk of 15 diseases. *Prev Med.* 2004;38:613-619.
 *Continuous models indicate a very slight J shape with the nadir for ischemic stroke at 15 g/d and for hemorrhagic stroke at 3 g/d, but "moderate" drinkers (25 g/d) were not found to be significantly different from abstainers in the categorical models.

uses of alcohol and the rhetoric surrounding both, it should not be surprising that ideological, political, and economic forces and vested interests play important roles in how alcohol is studied with respect to both

benefits and harms associated with its use. In contemporary times, these strong and sometimes exceedingly powerful opposing forces meet over the assertion that "moderate drinking" is beneficial to health because, of course, such an assertion has massive political and economic ramifications. It is therefore incumbent for scientists in this field to devote themselves not to proving an assertion but to questioning it and to remain free, to the extent possible, of identification with any of these strong influences. Such caution is warranted among scientists when alcohol is the topic of inquiry, regardless of whether the study is on the biological, behavioral, population, or institutional level.

Our own group's position on the health benefits of alcohol results from extensive discussion among ourselves and what seemed to us to be a herculean effort to eliminate—rather than prove—the Shaper, Wannamethee, and Walker hypothesis (1). On the basis of the fine contributions of laboratory science demonstrating plausible and real mechanisms for cardiac protection, our conclusion is that alcohol (among other substances, lifestyles, and behaviors) conveys benefit to the heart. But the lot falls to epidemiology to establish whether, in fact, human populations will benefit greatly from the use of alcohol and if they should be advised to use the substance for medicinal purposes. With others (15), we conclude that the actual outcomes in human populations for cardiac benefit have been exaggerated and we rely on Feinstein (65) for succinctly stating some of the problems facing contemporary epidemiology, alcohol-related epidemiology included: "The people who struggle to understand those results can be helped by recalling the old adage that statistics are like a bikini bathing suit: what is revealed is interesting; what is concealed is crucial."

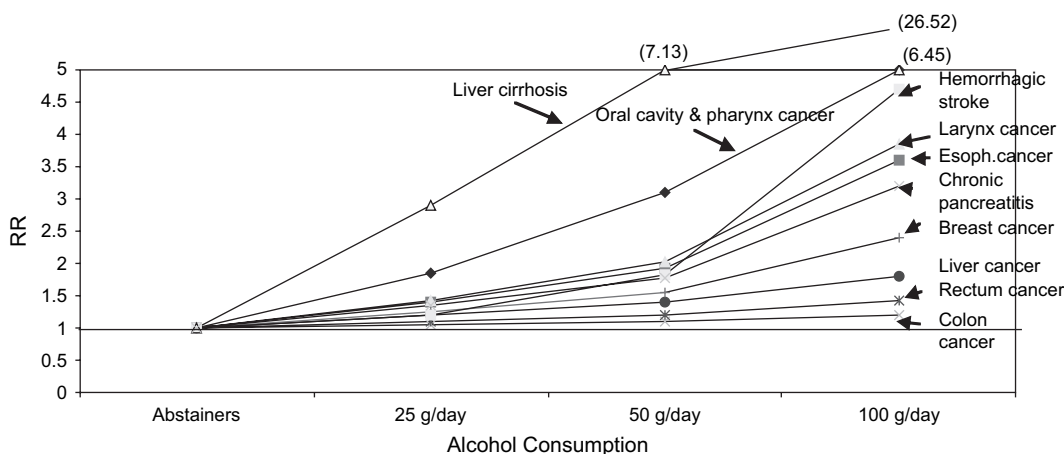


FIGURE 1. Significant associations of alcohol use with disease outcome. All diseases dominated by case-control studies ($\geq 66\%$) of the studies evaluated. (From Corrao G, Bagnardi V, Zambon A, La Vecchia C. A meta-analysis of alcohol consumption and the risk of 15 diseases. *Prev Med.* 2004;38:613-619.)

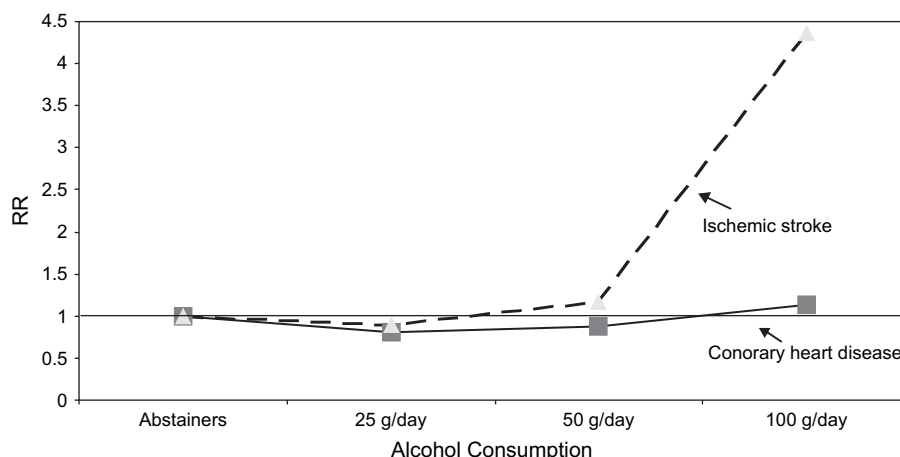


FIGURE 2. Significant associations of alcohol use with disease outcome. All diseases dominated by prospective studies ($\geq 50\%$) of the studies evaluated. (From Corrao G, Bagnardi V, Zambon A, La Vecchia C. A meta-analysis of alcohol consumption and the risk of 15 diseases. *Prev Med.* 2004;38:613–619 [essential hypertension also evaluated but, in essence, only one study was included in the evaluation, insufficient for comparison in our study].)

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