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Alcohol Consumption and Mortality in Patients With Cardiovascular Disease

A Meta-Analysis

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Objectives The purpose of this study was to quantify the relation between alcohol consumption and cardiovascular and total mortality in patients with a history of cardiovascular events.

Background Regular, moderate alcohol consumption by healthy people is associated with lower cardiovascular and all-cause mortality. No extensive meta-analysis is presently available on the possible association of alcohol consumption with secondary events in patients with cardiovascular disease.

Methods Articles were retrieved through October 2009 by search in PubMed and EMBASE. Fifty-four publications were identified, but only 8 were selected for our analyses, including 16,351 patients with a history of cardiovascular disease. Secondary events were cardiovascular or all-cause mortality. All selected studies were prospective. Data were pooled with a weighted, least-squares regression analysis of second-order fractional polynomial models.

Results The meta-analysis on cardiovascular mortality showed a J-shaped pooled curve with a significant maximal protection (average 22%) by alcohol at approximately 26 g/day. In the meta-analysis on mortality for any cause, J-shaped pooled curves were observed in the overall analysis (average maximal protection of 18% in the range of 5 to 10 g/day) and in all subgroups according to either the type of patients or the characteristics of the studies.

Conclusions In patients with cardiovascular disease, light to moderate alcohol consumption (5 to 25 g/day) was significantly associated with a lower incidence of cardiovascular and all-cause mortality. (J Am Coll Cardiol 2010;55: 1339–47) © 2010 by the American College of Cardiology Foundation

Moderate, regular alcohol consumption by apparently healthy people is associated with lower cardiovascular morbidity and mortality than in abstainers (1–6). Mechanisms supporting this include beneficial regulation of lipids and fibrinolysis, decreased platelet aggregation and coagulation factors, beneficial effects on endothelial function, and inflammation and insulin resistance (7–9). The proposed mechanisms of the beneficial role of drinking in moderation in healthy people may be similarly effective in people with a history of cardiovascular disease (CVD).

The abuse of alcohol is unquestionably harmful (2,3,6,10); in fact, the relationship between alcohol consumption and ischemic cardiovascular events or all-cause mortality in healthy people has been depicted as a J-shaped curve attributed to a dose-related combination of beneficial and harmful effects (1,11,12). The nonlinear J-shaped dose-response curve supports the hazards of excess drinking, but also indicates the potential windows of alcohol consumption that may confer a net beneficial effect, at least in terms of survival for apparently healthy subjects.

The 2006 Diet and Lifestyle Recommendations Scientific Statement from the American Heart Association Nutrition Committee (13) advises: "If you consume alcohol, do so in moderation (equivalent of no more than one drink for women or two drinks for men per day)." This is widely accepted within the scientific community, definitely when referring to healthy people. However, some concern has been raised of late regarding whether it is advisable to encourage people to drink small amounts regularly rather than abstain completely, especially among poor populations and in low-income countries where the disease burden per unit of alcohol consumption seems to be greater (10,14).

It is fundamental to prevent ischemic recurrences in survivors of primary cardiovascular events. Among the factors contributing to prevention, improving lifestyle and dietary

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Abbreviations and Acronyms

AMI = acute myocardial infarction

CVD = cardiovascular disease

RR = relative risk

SE = standard error

habits play a major role. However, guidelines in this area (15,16) are based on studies of apparently healthy subjects, on only few studies in cardiovascular patients, or both. Other recommendations about alcohol consumption in patients with previous CVD are based on experts' consensus rather than circumstantial evidence (17). The United States Food and Drug Administration warns that heart disease patients should stop drinking and that people who take aspirin regularly should not drink alcohol (18). However, in the 2006 American Heart Association/American College of Cardiology Guidelines for Secondary Prevention (16), CVD patients are encouraged to maintain a lifestyle that includes alcohol in moderation.

Several observational studies evaluated the association between alcohol intake and secondary events in CVD patients (19). One meta-analysis that examined the relationship between dietary changes and mortality in patients with coronary artery disease reported a reduction in all-cause mortality risk in moderate drinkers (20).

We present here the findings from 2 meta-analyses assessing the relationship between alcohol drinking and either fatal cardiovascular events or mortality for any cause in patients with a history of cardiovascular events. Our work extends that of Iestra et al. (20) because we included more recent studies and correlated alcohol intake by patients with established coronary artery disease with cardiovascular mortality in addition to total mortality. Moreover, current issues in epidemiology of alcohol consumption and health will be discussed.

Methods

Search strategy and data extraction. Articles were retrieved through October 2009 by searching in PubMed and EMBASE using the following key words: *cardiovascular disease* or *patients* in combination with *alcohol*, *wine*, *beer*, and *spirits* and with *mortality*, *morbidity*, *survival*, *death* (as Medical Subject Heading terms or text word), supplemented by references from the selected articles. Fifty-four publications were identified. Two of us independently reviewed them and selected 8 studies (21–28) of patients with a history of CVD. Studies were excluded if the qualifying primary event was different from coronary heart disease, AMI, or stroke; if only one category of alcohol intake was reported, or if it was not possible to extract quantitative data on alcohol consumption or if they were multiple reports (in that case, the report with the longer follow-up was used) (Fig. 1).

Secondary events included cardiovascular or all-cause mortality. As far as primary events are concerned, 7 studies included patients with previous CVD (1 stroke [24], 1 coronary heart disease [26], 5 AMI [21–23,25,28]), and 1 diabetic patient with a history of coronary heart disease (27)

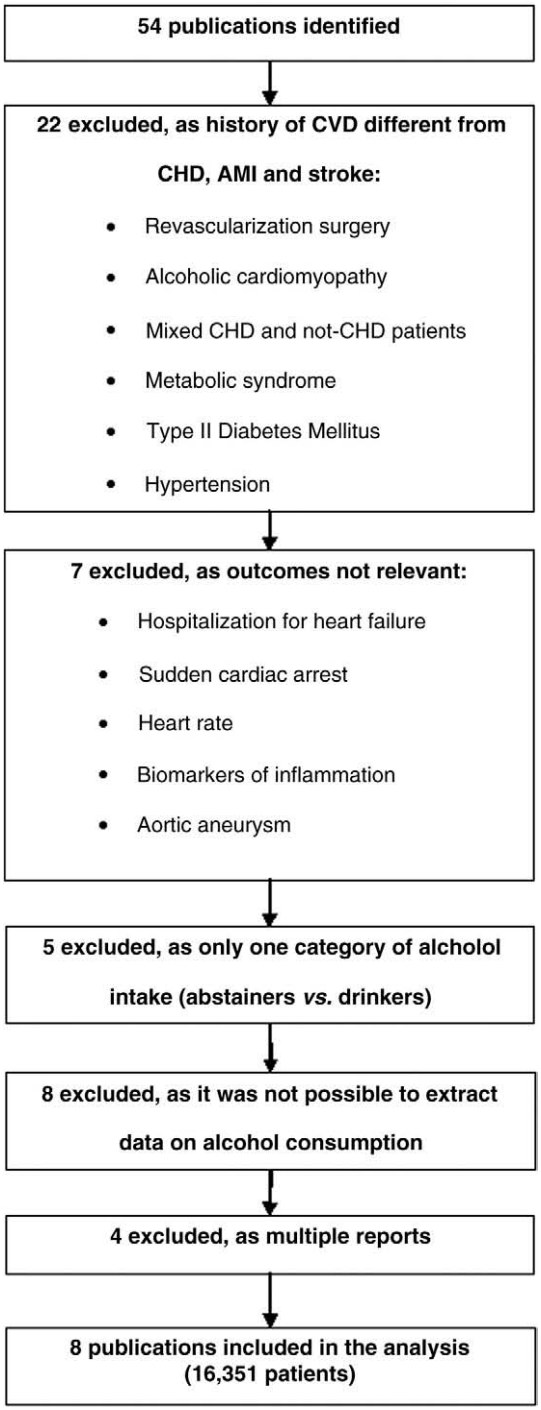

Figure 1 Flow Chart of the Selected Studies

AMI = acute myocardial infarction; CHD = coronary heart disease.

(Table 1). All selected studies were prospective (5 cohort studies [21,22,25–27]), and 3 were studies primarily designed as randomized control trials for specific drug therapy in CVD patients (23,24,28). Seven studies reported results separately for all-cause and cardiovascular mortality

Table 1 Characteristics of the 8 Studies Included in 1 or Both Meta-Analyses

First Author, Year (Ref. #)	Country	Follow-Up (yrs)	n	Primary Event	Secondary Event	When Questionnaire Administered	Former Drinkers in Reference Group	Sex	Meta-Analysis Inclusion
Janszky et al., 2008 (21)	Sweden	8.6	1,332	AMI	CV-M, AC-M	A	Yes*	M, F	Both
Masunaga et al., 2006 (22)	Japan	1.1	3,845	AMI	AC-M	A	No	M	Total mortality
Aguilar et al., 2004 (23)	USA	3.5	2,036	AMI	CV-M, AC-M	B	Not stated	M, F	Both
Jackson et al., 2003 (24)	USA	4.5	1,320	Stroke	CV-M, AC-M	B	Not stated	M	Both
Mukamal et al., 2001 (25)	USA	3.8	1,913	AMI	CV-M, AC-M	A	Yes	M, F	Both
Shaper et al., 2000 (26)	England	12.8	596	CHD	CV-M, AC-M	B	No	M	Both
Valmadrid et al., 1999 (27)	USA	12.3	266	CHD	CV-M	B	No	M, F	CVD mortality
Muntwyler et al., 1998 (28)	USA	5.0	5,356	AMI	CV-M, AC-M	B	Not stated	M	Both

*Exclusion of ex-drinkers in reference group in sensitivity analysis.

A = few days after the primary event; AC-M = all-cause mortality; AMI = acute myocardial infarction; B = more than 2 months after the primary event; CHD = coronary heart disease; CVD = cardiovascular disease; CV-M = cardiovascular mortality.

(21,23–26,28), 1 for all-cause mortality only (22), and 1 for CVD mortality only (27). With reference to alcohol consumption, all studies were observational. We performed 2 meta-analyses: the first included 7 studies reporting secondary risk of cardiovascular mortality and the second considered 7 studies reporting secondary risk of mortality for any cause (Table 1).

The size of a drink was taken as quantified in each article, except in 2 American studies (23,28) where a size of 14.0 g ethanol was chosen, according to the International Center for Alcohol Policies guidelines (29). In 3 studies (22,26,27) former drinkers were excluded formally from the reference group of life-long abstainers or nondrinkers, whereas in 2 studies, they were not (21,25) (in one of these, the authors performed a sensitivity analysis excluding former drinkers from the reference group (21)); in the remaining 3 studies (23,24,28), no statement about the reference group was made (Table 1).

Data analysis. We collected the following data: 1) the value x of alcohol (grams per day) assigned as the midpoint of the ranges (x was defined as 1.2 times the lower boundary for the open-ended upper categories [30]; our results did not change on multiplying the lower boundary for the open-ended upper categories by 1.0 or 1.4 or 1.6 instead of 1.2 [data not shown]); 2) frequency counts, adjusted relative risk (RR), and 95% confidence intervals for each x level; and 3) covariates describing the characteristics of the study. Inverse-variance–weighted methods that account for within-study correlation estimates were used (30). The models to be fitted were selected among fractional polynomial curves of the second order (31), considering power transformations of a continuous variable restricted to a predefined set of exponents (32). The regression models were $\log(\mathrm{RR}|x) = \beta_1 x^p + \beta_2 x^q$ and p and q were selected out of the set $(-2, -1, -0.5, 0, 0.5, 1, 2)$, after fitting multiple models. When $p = 0$, x^p is replaced by $\log(x)$, and when $p = q$, the model becomes $\log(RR|x) = \beta_1 x^p + \beta_2 x^q \log(x)$ (32). The best fit for p and q was defined as that with the highest likelihood.

To consider differences between studies as a further source of random variability, an additional component of the variance was added in weighing each observation (random effects). When there was heterogeneity, that is, when random and fixed solutions significantly differed, the analyses were carried out excluding one study at a time, and the deviances of random and fixed models were examined; a study was eliminated if its inclusion in the meta-analysis severely increased the deviances. Comparison of 2 hierarchical models was tested by the likelihood ratio test including or not in the models the interaction terms between the covariates (sex, type of primary event, design of the reference group) and alcohol intake (volume). Estimations of the metrics "maximal protection" and "reversion point" from the pooled dose-response curves were used to help data interpretation. Imprecision in the evaluation of these metrics from fitting of data is unavoidable; thus, point estimates of these parameters should not be emphasized. Pairwise contrasts were adjusted following the method of Sidak. All analyses were carried out using an SAS macro (SAS version 9.1.3 for Windows, SAS Institute, Cary, North Carolina) (32).

The hypothesis that publication bias may affect the validity of the estimates was tested by a funnel-plot–based approach. A simple test of asymmetry of the funnel plot was used according to the method proposed by Egger et al. (33). The symmetry of funnel plots was measured applying the following linear model: $RRj/se(RRj) = \alpha + \gamma 1/se(RRj)$, where $RRj/se(RRj)$ is the standard normal deviate (relative risk divided by its standard error), $1/se(RRj)$ is the precision of the estimate, and α and γ are the unknown parameters of the model.

The basic idea of this method is that, in the absence of publication bias and therefore in the presence of a symmetric funnel plot, the points will scatter about a line that runs through the origin. In this situation, an estimate of the parameter α would be found nearly equal to 0.

Results

Alcohol intake and cardiovascular mortality in CVD patients. From 7 studies (21,23–28) comprising 12,819 CVD patients (Tables 1, 2), we obtained 7 dose-response–independent relationships for alcohol and cardiovascular mortality. Symmetric funnel plots ($\alpha = 0$) were obtained for

JACC Vol. 55, No. 13, 2010
March 30, 2010:1339–47

Table 2 Characteristics and Results of the Best-Fitting Models: Meta-Analysis of Alcohol Intake and Cardiovascular Mortality

Subgroup	No. of Curves	n	Maximal Protection		Reversion Point* (g/day)	Parameters of the Best-Fitted Model = LogRR = $\beta_1\sqrt{x} + \beta_2\sqrt{x}$*log($x$)				p Value for Difference
			% (95% CI)	g/day		β_1 (SE)	p Value	β_2 (SE)	p Value	
All studies										0.002
Random model	7	12,819	26 (13–37)	8	24	−0.215 (0.088)	0.008	0.052 (0.031)	0.047	
Fixed model	7	12,819	22 (13–30)	8	26	−0.181 (0.058)	< 0.001	0.044 (0.021)	0.017	
Sex										0.90
Men	3	7,272	21 (11–31)	13	23	−0.161 (0.072)	0.013	0.036 (0.026)	0.08	
Both sexes	4	5,547	25 (9–38)	8	18	−0.219 (0.098)	0.013	0.058 (0.035)	0.049	
Type of primary event										
AMI	4	10,637	19 (8–28)	12	24	−0.136 (0.065)	0.018	0.031 (0.023)	0.092	
Type of reference group										
Without former drinkers	3	2,110	47 (27–62)	5	18	−0.538 (0.165)	0.019	0.157 (0.059)	0.077	
Alcohol intake questionnaire administration										
More than 2 months after the primary event	5	9,574	21 (11–29)		24	−0.158 (0.067)	0.009	0.037 (0.025)	0.067	

*The reversion point is defined as the dose of alcohol at which protection against total mortality is no longer statistically significant at the 95% confidence level.
AMI = acute myocardial infarction; CI = confidence interval.

all the categories of alcohol intake, showing the absence of publication bias (Fig. 2A).

The overall relationship between cardiovascular mortality and alcohol intake was interpreted as a J-shaped curve (Fig. 3), showing a protective effect (average 22%) that was maximal in the range of 5 to 10 g/day and still was significant up to approximately 26 g/day (Table 2 and Fig. 3, fixed model).

The best-fitting model was obtained when $p = q = 0.5$, corresponding to the model: $\log RR = \beta_1\sqrt{x} + \beta_2\sqrt{x}$*log($x$), for both the fixed and random models (Fig. 3). The deviances of fixed and random effects models fell from 22.30 to 12.60 ($p = 0.002$ for difference), suggesting heterogeneity among studies. The fitted parameters for the fixed model were $\beta_1 = -0.181$ (SE = 0.058; $p < 0.001$) and $\beta_2 = 0.044$ (SE = 0.021; $p = 0.017$) (Table 2). In subsequent analyses, using a fixed effects model with $p = q = 0.5$, we explored the possible role of study characteristics in explaining the interstudy heterogeneity.

Three studies reported results on men only and 4 included both men and women; the subgroup analysis showed no difference between the 2 groups of studies ($p = 0.90$) (Table 2). Pooled analyses of 3 studies (21,26,28) that excluded former drinkers from the reference category confirmed the protection of moderate alcohol consumption against cardiovascular mortality (Table 2).

Alcohol intake questionnaires were administered quite late (more than 2 months) after the qualifying event in 5 studies (23,24,26–28), but after only a few days in 2 studies (21,25). In the first group of studies, a J-curve was confirmed, with a shape very similar to that obtained using all studies on CVD patients (Table 2). Similar results were found considering only studies on patients with a previous AMI (Table 2).

Alcohol intake and mortality for any cause in CVD patients. Seven studies (21–26,28), comprising 16,398 patients with previous CVD (Tables 1 and 2), provided 9 dose-response independent relationships for alcohol intake and mortality from any cause. In this meta-analysis, too, publication bias was absent (Fig. 2B).

Two studies reported results separately for 2 age groups (22,28), and each contributed with 2 curves. The best-fitting model was obtained when $p = q = 0.5$ for both the fixed and random models (Table 3). Deviances of fixed and random effects models fell from 119.63 to 20.72 ($p < 0.001$ for difference), indicating heterogeneity among studies. After exclusion of a Japanese study (22), deviances of fixed and random effects models fell to 30.90 and 12.29, respectively ($p < 0.001$ for difference). In both the random and fixed-effects models, an overall J-shaped curve was obtained from the remaining 7 adjusted dose-response curves (Table 3, Fig. 4); the maximal protection was 20% and 18% in a range of 5 to 10 g/day in a random and fixed-effects model, respectively. Four studies included men only and 3 studies included both men and women; the subgroup analysis showed no difference between these 2 groups of studies ($p = 0.47$) (Table 3).

Similar results were found considering only studies of patients with a previous AMI (Table 3). Four studies gathered information on alcohol consumption late after the qualifying cardiovascular event (>2 months) (23,24,26,28). In these studies, a J-shape curve was confirmed, with 24% maximal risk reduction at approximately 8 g/day and significant protection up to approximately 24 g/day (Table 3). Six studies (12,553 patients) reported data both for cardiovascular and all-cause mortality (21,23–26,28). The 2 J-shaped curves overlapped at light consumption (6 to 12 g/day), showing maximal protection of approximately 20% (Fig. 5).

Discussion

The main novelty of the findings presented here is that—as in apparently healthy subjects—in CVD patients too, light to moderate drinking (5 to 15 g/day of alcohol) is associated

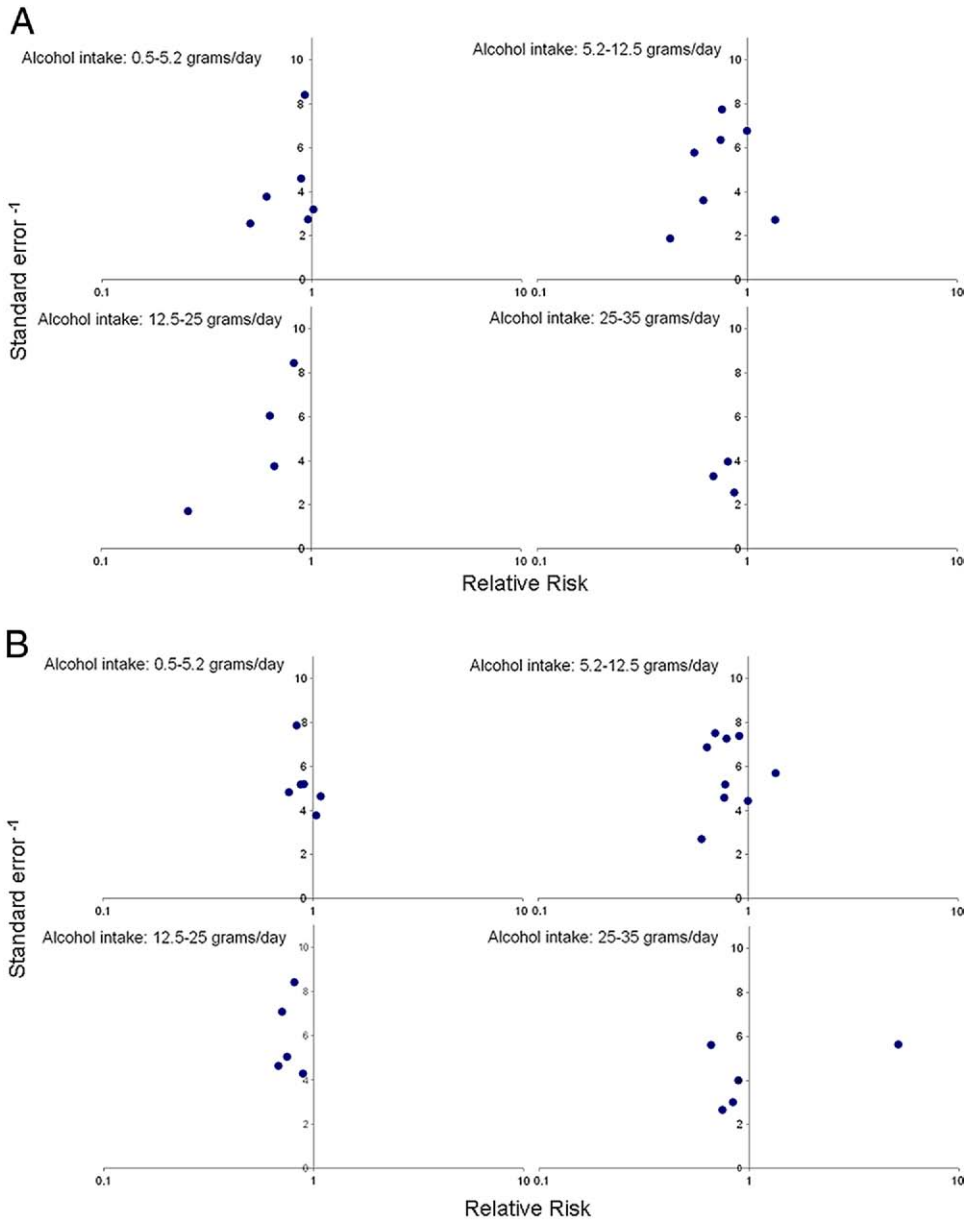

Figure 2 **Funnel Plots of the Selected Studies for Both Meta-Analyses**

Funnel plots for different alcohol intake categories (0.5 to 5.2 g/day, 5.2 to 12.5 g/day, 12.5 to 25 g/day, 25 to 35 g/day) for both meta-analyses. **(A)** Alcohol intake and cardiovascular mortality in cardiovascular disease (CVD) patients. **(B)** Alcohol intake and mortality for any cause in CVD patients.

with significant cardiovascular or all-cause mortality risk reduction, or both. In both our meta-analyses, a significant association with reduced risk was found up to 25 g/day of alcohol. The J-shaped relationship between alcohol intake and total mortality was comparable with that previously reported in apparently healthy individuals (11) and can be explained as a dose-related combination of both beneficial and harmful effects. If alcohol intake within a relatively large range is inversely related to CVD, increasing alcohol consumption is reportedly associated with an increasing risk of certain cancers, cirrhosis, and death from accidents (2,11). When alcohol use was recorded somewhat late after diagnosis of the primary event (more than 2 months), probably reflecting the real intake of alcohol before a secondary event, the protective effect of moderate alcohol consumption was confirmed by both meta-analyses.

From the 6 studies that reported data on both cardiovascular and all-cause mortality, 2 similar dose-response curves were obtained (Fig. 5). Most likely, as in patients with previous CVD, the main cause of death is a secondary fatal cardiovascular event; the reduction in cardiovascular risk by

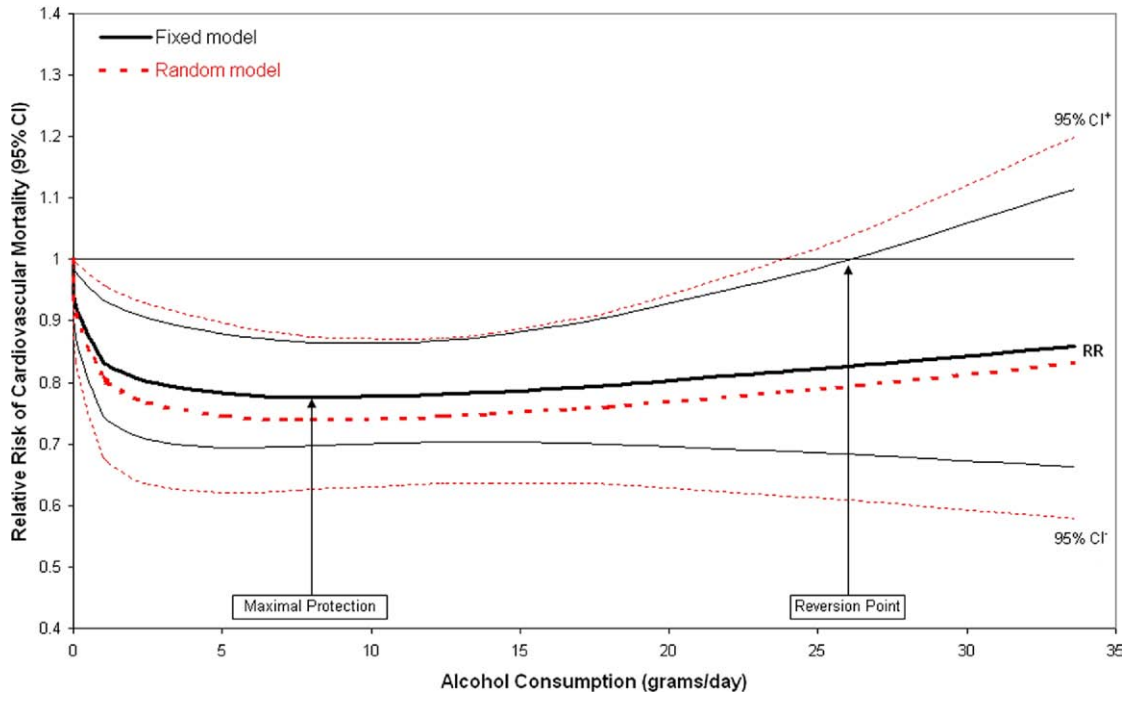

Figure 3 Alcohol Consumption in Relation to Cardiovascular Mortality in Cardiovascular Disease Patients

Pooled curves of relative risk of cardiovascular mortality and alcohol intake, extracted from 7 independent relationships using fixed **(solid lines)** and random **(dotted lines)** models. RR = relative risk; 95% CI$^-$ = lower value of confidence interval; 95% CI$^+$ = upper value of confidence interval.

moderate alcohol consumption would prevail over the less frequent noncardiovascular fatal events.

In patients with CVD, the potential interactions with alcohol have been investigated mainly for antiplatelet or oral anticoagulant drugs (34). Alcohol and medications interact in a variety of situations; absorption, distribution, or metabolism of the alcohol, medications, or both may be altered, affecting the therapeutic and adverse effects of the latter (34,35). A sensitive analysis with adjusted and nonadjusted studies for drug therapy (antiplatelet or oral anticoagulant drugs) was not possible in our meta-analyses because of limited available data.

Table 3 Characteristics and Results of the Best-Fitting Models: Meta-Analysis of Alcohol Intake and All-Causes Mortality

Subgroup	No. of Curves	n	Maximal Protection		Reversion Point* (g/day)	Parameters of the Best-Fitted Model = LogRR = $\beta_1\sqrt{x} + \beta_2\sqrt{x}$*log($x$)				P for Difference
			% (95% CI)	g/day		β_1 (SE)	p Value	β_2 (SE)	p Value	
All studies										< 0.001
Random model	9	16,398	22 (2–39)	2.5	8	−0.223 (0.114)	0.025	0.070 (0.039)	0.035	
Fixed model	9	16,398	24 (16–31)	2.5	15	−0.251 (0.085)	< 0.001	0.085 (0.016)	< 0.001	
Selected studies†										< 0.001
Random model	7	12,553	20 (9–30)	7	27	−0.147 (0.065)	0.012	0.033 (0.022)	0.070	
Fixed model	7	12,553	18 (10–25)	7	24	−0.153 (0.047)	< 0.001	0.040 (0.017)	0.008	
Sex†										0.47
Men	4	7,272	18 (8–28)	5	17	−0.172 (0.060)	0.002	0.050 (0.022)	0.010	
Both sexes	3	5,281	21 (8–33)	12	27	−0.147 (0.082)	0.036	0.032 (0.027)	0.121	
Type of primary event†										
AMI	5	10,637	22 (16–30)	12	32	−0.167 (0.053)	< 0.001	0.038 (0.018)	0.020	
Alcohol intake questionnaire administration†										
More than 2 months after the primary event	5	9,308	17 (7–25)	8	24	−0.135 (0.056)	0.008	0.034 (0.020)	0.045	

*The reversion point is defined as the dose of alcohol at which protection against total mortality is no longer statistically significant at the 95% confidence level. †Excluding the curves from the study of Masunaga et al. (22).

Abbreviations as in Table 2.

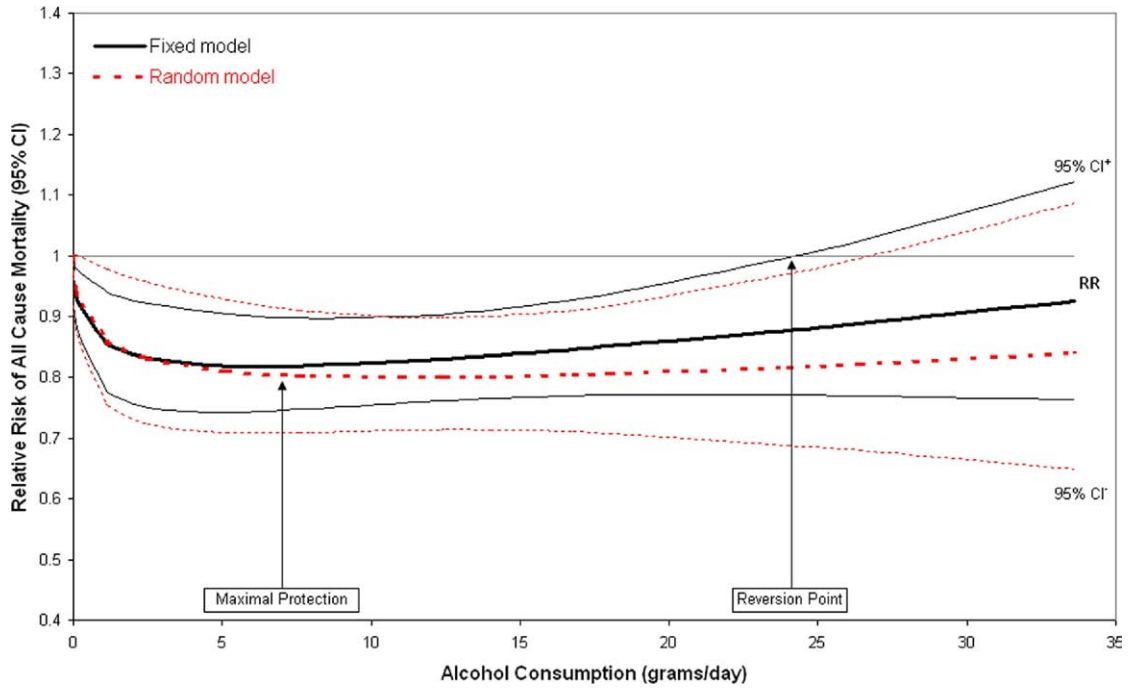

Figure 4 **Alcohol Consumption in Relation to All-Cause Mortality in Cardiovascular Disease Patients**

Pooled curves of relative risk of all-cause mortality and alcohol intake extracted from 7 independent relationships using fixed **(solid lines)** and random **(dotted lines)** models. Abbreviations as in Figure 3.

Study limitations. A first limitation of our findings is that, in the absence of randomized controlled trials, all the studies included in our meta-analyses were observational. Randomized controlled trials offer a more solid answer than observational studies to many questions in medicine, mainly restricted, however, to the efficacy of drugs; however, controlled intervention trials on diet in general and on alcohol in particular, are difficult and ethically questionable to perform (36,37).

Another limitation of our analyses is the small number of studies that could be included, especially when subanalyses on interstudy heterogeneity were performed. In addition, an appropriate control for confounding variables was applied in only a few of the original studies.

An obvious weakness of our analyses—because of lack of information from the original studies—is that in only a few instances was it possible to separate former drinkers from lifetime abstainers within the nondrinking group. The inclusion of former drinkers in the reference group who might have stopped because of health problems is questionable, and may explain, at least in part, the protective effect of drinking in moderation (1,36). However, analysis of the 3 studies (21,26,27) that formally excluded former drinkers from the no-alcohol category confirmed the relation between drinking in moderation and secondary prevention, too, as far as cardiovascular mortality was concerned.

Any meta-analysis can be plagued by publication bias, because even high-quality studies reporting negative results often are not submitted by investigators themselves or are not accepted for publication by editors. Thus, a formal analysis of publication bias was carried out: the funnel plots appeared to be symmetric for all the categories of alcohol intake, indicating the absence of publication bias in both our meta-analyses.

Under-reporting of alcohol consumption would result in a tendency for relative risks to be biased toward the null hypothesis, and this may have distorted the shape of the curves and the apparent threshold for harm; however, both meta-analyses showed significant association.

In the largest study included in our meta-analysis, The Physicians Health Study (28), the protection associated with alcohol in moderation was greater for non-CVD than for CVD deaths, an unexpected finding. In a subgroup analysis including the 2 studies only (26,28) for which data on non-CVD mortality were available, we could confirm such a finding (data not shown). Thus, the possibility of uncontrolled confounding by lifestyle, medicines, or other factors among the light-to-moderate drinking patients cannot be excluded, suggesting—at least in some studies—possible selection bias rather than a biological effect of alcohol (38).

Conclusions

Our findings provide reasonable evidence that regular and moderate alcohol intake is significantly associated with a

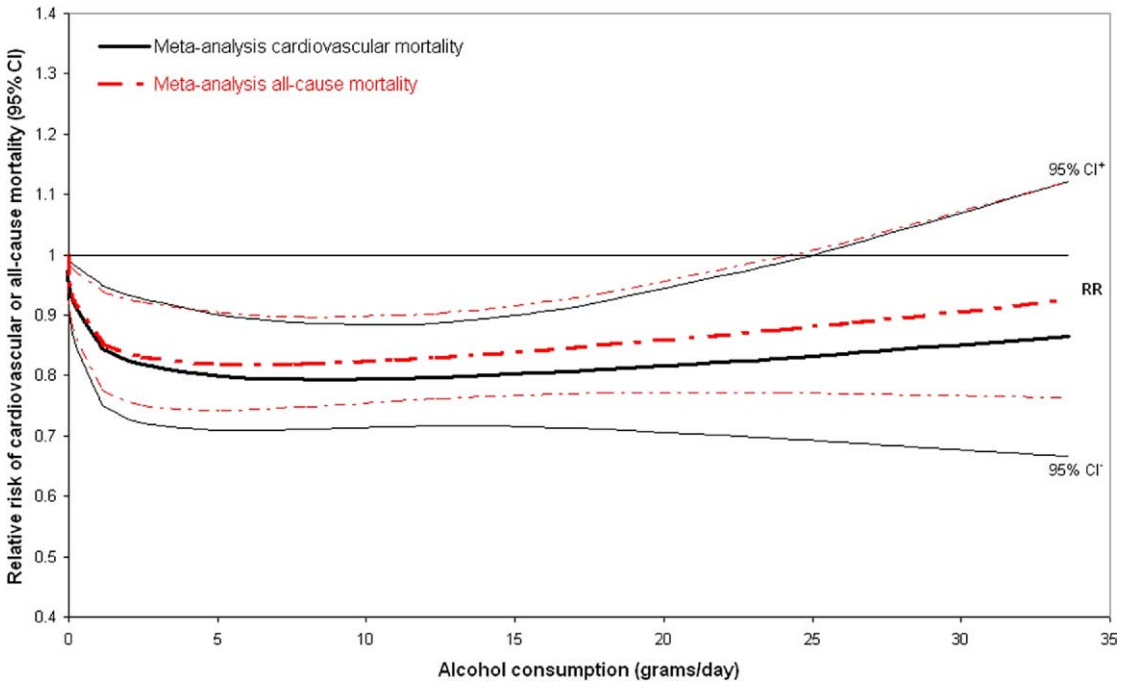

Figure 5 **Comparison Between Curves on Cardiovascular and All-Cause Mortality in Cardiovascular Disease Patients**

Curves for vascular **(dotted lines)** and all-cause **(solid lines)** mortality among patients with previous coronary or cerebrovascular events, extracted from the same cohort studies (21,23–26,28). Abbreviations as in Figure 3.

reduction in the incidence of secondary cardiovascular events and all-cause mortality. This conclusion extends to CVD patients what has been reported previously in apparently healthy people (1,11).

Cardiovascular patients should be informed that low-to-moderate alcohol consumption (1 drink/day for women or up to 2 drinks/day for men), should not be harmful to their health. However, cardiovascular patients who do not regularly consume alcohol should not be encouraged to start drinking, owing to the lack of controlled intervention trials on alcohol that are difficult and ethically questionable to perform. No question, heavy or binge drinking can have adverse health outcomes (10). If cardiovascular patients are heavy drinkers, they must strongly be advised to abstain or at least substantially reduce drinking.

Cardiologists should be aware that regular, moderate alcohol consumption, in the context of a healthy lifestyle (increased physical activity, no smoking), dietary habits (decreased dietary fat intake, high consumption of fruit and vegetables), and adequate drug therapy, would put their patients at a level of cardiovascular or mortality risk substantially lower than either abstainers or heavy or binge drinkers.

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