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Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors

Eric B Rimm, Paige Williams, Kerry Fosher, Michael Criqui, Meir J Stampfer

Abstract

Objective To summarise quantitatively the association between moderate alcohol intake and biological markers of risk of coronary heart disease and to predict how these changes would lower the risk.

Design Meta-analysis of all experimental studies that assessed the effects of moderate alcohol intake on concentrations of high density lipoprotein cholesterol, apolipoprotein A I, fibrinogen, triglycerides, and other biological markers previously found to be associated with risk of coronary heart disease.

Participants Men and women free of previous chronic disease and who were not dependent on alcohol. Studies were included in which biomarkers were assessed before and after participants consumed up to 100 g of alcohol a day.

Interventions Alcohol as ethanol, beer, wine, or spirits.

Main outcome measures Changes in concentrations of high density lipoprotein cholesterol, apolipoprotein A I, Lp(a) lipoprotein, triglycerides, tissue type plasminogen activator activity, tissue type plasminogen activator antigen, insulin, and glucose after consuming an experimental dose of alcohol for 1 to 9 weeks; a shorter period was accepted for studies of change in concentrations of fibrinogen, factor VII, von Willebrand factor, tissue type plasminogen activator activity, and tissue type plasminogen activator antigen.

Results 61 data records were abstracted from 42 eligible studies with information on change in biological markers of risk of coronary heart disease. An experimental dose of 30 g of ethanol a day increased concentrations of high density lipoprotein cholesterol by 3.99 mg/dl (95% confidence interval 3.25 to 4.73), apolipoprotein A I by 8.82 mg/dl (7.79 to 9.86), and triglyceride by 5.69 mg/dl (2.49 to 8.89). Several haemostatic factors related to a thrombolytic profile were modestly affected by alcohol. On the basis of published associations between these biomarkers and risk of coronary heart disease 30 g of alcohol a day would cause an estimated reduction of 24.7% in risk of coronary heart disease.

Conclusions Alcohol intake is causally related to lower risk of coronary heart disease through changes in lipids and haemostatic factors.

Introduction

The inverse association between moderate alcohol intake and coronary heart disease is documented in over 40 prospective studies in diverse populations.¹⁻⁵ Men and women who consume one to three drinks a day have a 10% to 40% lower risk of coronary heart disease than those who abstain. In most large studies risk of coronary heart disease decreases in a downward linear fashion with alcohol intake up to three drinks a day.⁶⁻⁹ This reduction is generally attributed to the beneficial effects of alcohol on lipids and haemostatic factors.^{5 10-13}

Over 75 experimental studies have examined the effects of alcohol intake on lipids, haemostatic factors, vitamins, glucose, insulin, and lipid peroxidation.^{10 w1-w55} However, only a few epidemiological studies have simultaneously examined the relation between alcohol intake, biochemical variables, and subsequent risk of coronary heart disease.^{w56-w61} From these studies it is estimated that half of the beneficial effect of moderate alcohol intake is due to increased high density lipoprotein cholesterol concentrations. This calculation may, however, be an underestimate because it does not take into account measurement error in the assessment of average alcohol intake or biological variability in high density lipoprotein cholesterol concentrations. In several of these studies potential confounding by other lifestyle factors—for example, diet, obesity, and physical activity—was also not considered. Furthermore, other biochemical variables, such as fibrinogen, triglycerides, von Willebrand factor, and insulin, were not examined in these simultaneous models.

We quantitatively summarised the effects of alcohol on a variety of biomarkers from experimental studies using standard meta-analysis methods, and we projected the impact of those changes on risk of coronary heart disease using data from published studies relating biomarker concentrations to coronary heart disease.

Methods

We searched Medline for all experimental studies of alcohol (ethanol) in humans published in English between 1965 and 1998. We supplemented our search by examining citations in review articles,^{1 3 14 15} the pro-

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ceedings of meetings and symposia, and the *Journal of the Alcohol Beverage Medical Research Foundation* and *Alcohol Research*—journals that track alcohol related research. We restricted our search to studies in individuals without diagnosed coronary heart disease, diabetes, or alcohol dependence. We included only those studies that assessed biomarkers consistently modified by alcohol and related to risk of coronary heart disease. For lipid factors we included only studies with an intervention period of at least seven days; shorter intervals seem to have little or no effect. We included all studies of coagulation and thrombolytic factors because effects have been documented within hours after consumption of alcohol. Although we describe studies of lipid peroxidation and platelet aggregation we did not include these in our quantitative analyses because these assays were not comparable across studies owing to major differences in methodology. Furthermore, most were assessed with in vitro assays, which have not consistently been linked to risk of coronary heart disease.

In the final analysis we included only studies that provided the number, age range, and sex of the participants, average dose of alcohol, duration of the study, beverage type (beer, wine, spirits, or ethanol), and the change in concentration of a biological marker compared with its pretreatment measurement or a comparable group of placebo or untreated participants. Data were abstracted by two of the authors, and differences were resolved through consultation.

We excluded studies where ≥ 100 g of ethanol were consumed a day. For studies with multiple doses or multiple subpopulations we abstracted a data record from each study subpopulation. If ethanol was provided on the basis of the participant's weight we calculated the amount of ethanol for the average weight of the study participants. In several studies alcohol was given within strata of obesity or physical activity. These factors were considered as potential modifiers of the underlying relation between ethanol and biological variables of coronary heart disease. In our analysis each subpopulation was considered as a separate data record.

Statistical methods

For each biological measure we fitted a zero intercept weighted linear regression model predicting the change in the biological marker for alcohol intake as a continuous variable. We fitted intercept models and models with higher order terms, but the results were not appreciably different from our main analyses and are not presented. Each study was weighted by the inverse of the variance of the change measure. If no variance measure was provided we computed the average weight from the remaining studies. For biological markers with fewer than 10 data records we weighted the regressions by the size of the study. Using other weighting schemes did not substantially change the main results.

Consistent with standard meta-analysis techniques we treated study (or subpopulation within study) as a random effect, inducing a mixed effects model structure. The weighted least squares regression analyses were performed with a proc mixed procedure (version 6.12, SAS Institute, Cary, NC) using the biological marker as the dependent variable and dose of alcohol,

age, sex, beverage type, and duration of study as the independent variables (fixed effects). In testing significance of each of the fixed effects we used Sattenthwaite's approximation to the degrees of freedom.^{16 17}

To estimate quantitatively the effect of alcohol on each biological marker we calculated the predicted mean change after an intake of 30 g of alcohol a day. Previously published studies linking each biomarker to risk of coronary heart disease were used to calculate the predicted relative risk of coronary heart disease that would be expected on the basis of the change in each biomarker achieved by consuming two drinks a day. Any association between a single biological measure and risk of coronary heart disease will usually be an underestimate of the true effect because of random error in biological measures owing to within person variability.^{18 19} To evaluate the influence of measurement error on our results we used previously published estimates of components of variation in biological measures^{20 21} to adjust the predicted relative risks for this error.

Results

After exclusions we reviewed 42 experimental studies of alcohol, providing 67 separate data records. For the main analysis we excluded six data records from studies in which participants who usually consumed alcohol were restricted from any intake for several weeks, because the baseline measure of alcohol is less precise than in studies in which standard amounts of alcohol were given.

High density lipoprotein cholesterol

Results on change in high density lipoprotein cholesterol concentrations were available from 36 data records from 25 studies (see table A on website). After consumption of an average 40.9 g of alcohol a day for 4.1 weeks, high density lipoprotein cholesterol concentrations increased by an average of 5.1 mg/dl. In an unweighted regression model high density lipoprotein cholesterol concentrations increased by 0.122 mg/dl per gram of alcohol a day (fig 1). After weighting each study as described high density lipoprotein cholesterol concentrations increased by 0.133 mg/dl per gram of alcohol consumed a day. The average individual consuming 30 g of alcohol a day would expect an increase in high density lipoprotein cholesterol concentration of 3.99 mg/dl (95% confidence interval 3.25 to 4.73) compared with an individual who abstains—an 8.3% increase from pretreatment values (fig 2).

Although we observed no significant confounding or modification of the effects of alcohol on high density lipoprotein cholesterol concentration by sex, duration of study, median age, or beverage type we did find some qualitative differences. Among men (29 records) the coefficient for a 1 g increase in alcohol was stronger ($b=0.134$ mg/dl) than in women (three records) ($b=0.095$ mg/dl; interaction, $P=0.93$). Among five studies with average baseline high density lipoprotein cholesterol concentrations below 40 mg/dl the effect of alcohol was stronger ($b=0.138$) than among the 18 studies with concentrations above 48 mg/dl ($b=0.110$; interaction, $P=0.04$). Among the five studies that

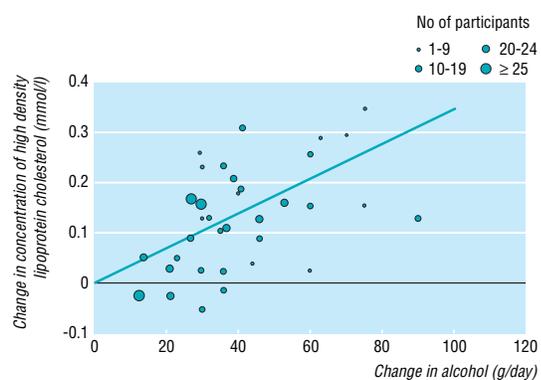


Fig 1 Weighted regression analysis of alcohol and high density lipoprotein cholesterol concentration from 36 data records abstracted from experimental studies of alcohol intake

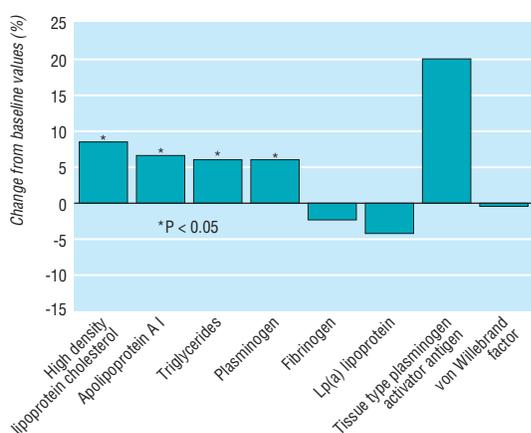


Fig 2 Percentage change in biomarkers associated with intake of 30 g of alcohol a day

selected physically fit participants the effect of alcohol was weaker ($b = 0.108$) than in the four studies of sedentary participants ($b = 0.190$; interaction, $P = 0.45$). The coefficients for alcohol from beer ($b = 0.160$; 13 studies), wine ($b = 0.132$; 11), and spirits ($b = 0.111$; 4) were not significantly different from each other or from the coefficient among the remaining studies that provided either ethanol or non-specific alcohol containing beverages ($b = 0.128$; 8).

Apolipoprotein A I

An average of 37.6 g of alcohol a day was consumed for 3.9 weeks resulting in an increase in apolipoprotein A I concentrations of 11.83 mg/dl. After weighting each of the 24 data records we found a 0.294 mg/dl increase in apolipoprotein A I concentrations per gram of alcohol consumed a day ($P < 0.001$). The average individual consuming 30 g of alcohol a day showed an 8.82 mg/dl (7.79 to 9.86) increase in apolipoprotein A I concentrations (6.5% increase over baseline; fig 2).

Triglycerides

From 35 data records we found that triglyceride concentrations increased by 0.19 mg/dl per gram of alcohol consumed a day ($P = 0.001$) and 5.69 mg/dl

(2.49 to 8.89) per 30 g consumed a day (5.9% increase over baseline; fig 2).

The coefficient for alcohol was stronger among the 26 studies in men ($b = 0.22$; $P = 0.003$) than among the three studies in women ($b = -0.09$; $P = 0.41$), but the small number of studies conducted only among women limits our power to observe differences. The coefficient for 11 studies with only beer ($b = 0.27$) was slightly stronger than the coefficient for 11 studies with only wine ($b = 0.20$) and for six studies with only spirits ($b = 0.17$), but the differences were not significant.

Other factors

Alcohol intake has been associated with a favourable thrombolytic profile in many cross sectional studies^{12 13 22-25} and in several experimental studies (see table B on website). Many studies have used in vitro or ex vivo measures of platelet aggregation, but assay methods vary greatly and few such markers have been linked with risk of coronary heart disease. Only a few studies have assessed concentrations of fibrinogen, plasminogen, tissue type plasminogen activator, plasminogen activator inhibitor-1, factor VII, and von Willebrand factor (see table B on website)—factors that have been associated with risk of coronary heart disease.²⁶⁻²⁸ Weighted regression analyses for each of these haemostatic factors was suggestive of a more thrombolytic profile, but none was significantly affected by moderate alcohol intake (fig 2). From the weighted regression equations an increment of 30 g of alcohol a day was associated with a 7.5 mg/dl (-17.7 to 32.7) decrease in fibrinogen concentration, a 1.25 ng/ml (-0.31 to 2.81) increase in tissue type plasminogen activator antigen concentration, and a 1.47% (-1.18 to 4.42) increase in plasminogen concentration. Lp(a) lipoprotein—a lipoprotein particle that may affect the fibrinolytic cascade—was only assessed in four studies (five data records) and was modestly, and non-significantly, decreased by 0.70 mg/dl (-3.38 to 1.99) for each 30 g increment of alcohol a day. We did not include activity of tissue type plasminogen activator owing to substantial differences in assay methods and heterogeneity of results. Furthermore, it is not clear that acute changes in tissue type plasminogen activator caused by alcohol intake should be used to determine subsequent risk of coronary heart disease because concentrations may also be influenced by extent of existing coronary disease.²⁷ Sufficient data were not available to calculate a weighted average for von Willebrand factor or factor VII, but alcohol tended to lower the concentrations of both.^{w37 w50}

The effect of alcohol on many other biochemical variables (for example, insulin, glucose, carotenoids, folate, lipid peroxidation, low density lipoprotein cholesterol, apolipoprotein B) has been assessed, but we excluded from this analysis those risk factors that had not been consistently found to be altered by alcohol, for which fewer than four data records were available, or that had not been consistently linked to risk of coronary heart disease.

Quantitative prediction of reduction in coronary heart disease risk among moderate drinkers

Using the effect sizes estimated for a 30 g increase in alcohol intake a day and results from studies of

Projected percentage reduction in risk of coronary heart disease attributed to effects of alcohol on concentrations of high density lipoprotein cholesterol, fibrinogen, and triglycerides

Biomarker	Relative risk (95% CI) from published study	Projected reduction in coronary heart disease associated with 30 g alcohol per day versus abstaining (%)	
		Unadjusted	Adjusted for intraindividual variability
High density lipoprotein cholesterol	0.69 (0.47 to 0.99) per 10 mg/dl ³²	13.5	16.8
Fibrinogen	1.34 (1.15 to 1.56) per 50 mg/dl ²⁹	4.3	12.5
Triglycerides	1.40 (1.10 to 1.77) per 100 mg/dl ³³	-1.9	-4.6
Total		15.9	24.7

biological markers and risk of coronary heart disease we computed the expected change in risk associated with consuming 30 g of alcohol a day compared with abstaining. No single epidemiological study has simultaneously calculated the risk of coronary heart disease associated with all biological markers. Therefore, we used several similar studies,²⁶⁻³¹ which provided multivariate relative risk estimates for differences in concentrations of high density lipoprotein cholesterol, apolipoprotein A I, triglycerides, and fibrinogen (table).

The average increase in high density lipoprotein concentrations of 3.99 mg/dl for an intake of 30 g of alcohol a day would be associated with a risk reduction of 13.5% (4.3% to 24.2%) among men in the physicians' health study²⁹; a similar reduction of 13.3% (10.6% to 15.9%) would be expected on the basis of results from the lipids research clinics study.³² If we adjust the effect estimate for intraindividual variability in high density lipoprotein cholesterol concentrations²⁰ we estimate a 16.8% reduction in risk of coronary heart disease directly attributable to increased high density lipoprotein cholesterol concentration from consuming 30 g of alcohol a day. Because the effect of alcohol on high density lipoprotein cholesterol concentration was stronger in those with lower baseline concentrations the predicted 5.09 mg/dl increase for those with an average concentration of 35 mg/dl would lower the risk of coronary heart disease by 20.9% after adjustment for intraindividual variability. Because concentrations of high density lipoprotein cholesterol and apolipoprotein A I are highly correlated, and the predicted reduction in risk was comparable for intakes of 30 g of alcohol a day, we assumed that the increase in concentrations of both markers were not independent and reflect the same biological phenomenon.

The small but consistent positive association between alcohol and triglyceride concentration may attenuate the benefits of alcohol. From the physicians' health study we project that the 5.69 mg/dl increase in triglyceride concentration from consuming 30 g of alcohol a day may increase the risk of coronary heart disease by 1.9% (0.5% to 3.3%); 4.6% after adjustment for intraindividual variability in triglyceride concentration.

Estimates of benefits of alcohol owing to haemostatic factors is less robust because fewer experimental studies have assessed these markers and, apart from fibrinogen, the results that link these biomarkers with risk of coronary heart disease are inconsistent. We predict a 7.5 mg/100 ml decrease in fibrinogen concentration associated with an intake of 30 g of alcohol

a day, but this decrease was not significant. Such a decrease, however, would lower the risk of coronary heart disease by 4.3% (2.0% to 6.5%) based on the Northwick Park study.²⁷ Adjusting the estimate for intraindividual variability, the predicted risk reduction for an intake of 30 g of alcohol a day would be 12.5%.

If high density lipoprotein cholesterol, fibrinogen, and triglycerides act independently to raise or lower the risk of coronary heart disease the overall benefit projected from consuming 30 g of alcohol a day would be 24.7% after adjustment for measurement error (table). This probably underestimates the true risk reduction associated with consuming 30 g of alcohol a day because it ignores the changes in concentrations of plasminogen, Lp(a) lipoprotein, insulin, platelet aggregation, factor VII, and von Willebrand factor.

Discussion

Summary of main findings

In this quantitative review we found strong and consistent evidence linking moderate alcohol intake with higher concentrations of high density lipoprotein cholesterol and apolipoprotein A I and lower concentrations of fibrinogen. We also found a weak association between moderate alcohol intake and increased triglyceride concentration. On the basis of published associations between these biomarkers and risk of coronary heart disease we calculated an overall predicted 24.7% reduction in risk of coronary heart disease associated with an intake of 30 g of alcohol a day owing to changes in these markers. These data support a causal interpretation of the association between moderate alcohol intake and lower risk of coronary heart disease and suggest that the benefit is mediated in part through several known biological markers of coronary heart disease. The data suggest, however, that other mechanisms are probably involved, but these could not be included in our analysis owing to lack of available experimental data.

Limitations

Our review has several limitations. Study methods and assay procedures varied. Even among studies that used similar methods changes in biological markers may be modified by differences in genetic predisposition and metabolic ability, diet, smoking patterns, or other lifestyle factors across populations. Unmeasured biological variability in response to moderate alcohol intake would attenuate our overall results. Furthermore, our results are based on experimental studies of short duration; data are not available to test whether similar effects would be found with longer studies. None the less, the 24.7% reduction in risk of coronary heart disease that we predict on the basis of an intake of 30 g of alcohol a day is comparable to relative risks reported from several large scale prospective studies of alcohol and coronary heart disease.^{4,6,9}

Meta-analyses based only on published data can produce spurious results if null findings or contradictory findings are less likely to be published. However, the intensive effort required for experimental studies of alcohol intake and the assessment of multiple biological outcomes make it less likely that results would go unpublished. In several studies, specific changes in biological markers before and after alcohol

intake were provided only for factors that substantially changed; those factors not appreciably altered by alcohol were only mentioned. For these data records we assumed the change to be zero.

Alcohol and other factors

Too few experimental studies included measures of insulin sensitivity for us to be able to summarise them. However, several large cross sectional studies have reported strong positive associations between alcohol and increased insulin sensitivity.^{33 34}

Most of the experimental studies were among young healthy populations. This may provide a better estimate of the true biological effects of moderate alcohol intake as the results are less likely to be influenced by pre-existing lipid abnormalities or preclinical disease. Conversely, the average percentage increase in triglyceride concentration (fig 2) may exaggerate any added health risk associated with moderate alcohol intake as the average baseline triglyceride concentrations were generally low in these populations (mean 96.3 mg/dl), and even a small absolute increase in triglyceride concentrations translates to a larger comparative change. The importance of the small increase in triglyceride concentrations is further complicated as increases may not be in the more atherogenic small dense very low density lipoprotein particles.

The association between alcohol and blood pressure has been extensively studied. Although heavy intake (more than four drinks a day) is associated with hypertension^{35 36} no clear dose response has been established at levels of moderate intake (30 g/day). In several prospective studies the relation is U-shaped or J-shaped³⁷ suggesting a slight decrease in blood pressure among those who consume one drink a day. The overall effect of moderate alcohol intake on blood pressure is likely to be minor; therefore we did not include blood pressure in our review.

Biological mechanisms

As reviewed in detail elsewhere^{10 38} alcohol may directly increase the hepatic production and secretion of apolipoproteins and lipoprotein particles, increase triglyceride lipase concentrations, and decrease removal of circulating high density lipoprotein cholesterol. The increase in production of extrahepatic lipoprotein lipases is in response to increased triglyceride concentrations. Lipolysis of triglyceride rich particles increases the flow of cholesterol to high density lipoprotein particles from circulating very low density lipoprotein remnants and raises overall high density lipoprotein concentration. Although speculative, alcohol may also interfere with the activity of cholesteryl ester transfer protein^{39 40} and reduce the transfer of cholesteryl esters in high density lipoprotein particles to more atherogenic particles. Some investigators have suggested that alcohol may preferentially increase high density lipoprotein-3 particles, which contain apolipoprotein A I and apolipoprotein A II.^{41 42} In the two experimental studies that we summarised, which specifically measured the apolipoprotein content of high density lipoprotein particles, both found an increase in high density lipoprotein particles with apolipoprotein A I and apolipoprotein A II,^{w30 w31} but Clevidence et al found a similar increase in high density lipoprotein particles only containing apolipo-

Key messages

- Results from observational studies provide strong evidence that moderate alcohol intake lowers risk of coronary heart disease
- Short term trials of alcohol intake show significant changes in concentrations of lipids and clotting factors
- The changes in concentrations of high density lipoprotein cholesterol, fibrinogen, and triglycerides associated with an intake of 30 g of alcohol a day should reduce risk of coronary disease by 24.7%
- Alcohol intake may be causally related to lower risk of coronary heart disease through changes in lipids and haemostatic factors

protein A I.^{w31} There were insufficient data from experimental studies of high density lipoprotein subcomponents to clarify this issue; none the less the importance of high density lipoprotein subfractions in risk prediction may be minimal if total high density lipoprotein concentration is considered.^{w31}

The effects of alcohol on the thrombolytic and coagulation processes are not as well described.^{5 12 13 25}

The mechanism by which alcohol decreases fibrinogen concentration is not known, although the effect has been documented in several large cross sectional studies^{33 43} as well as the small experimental studies described. Alcohol inhibits induced platelet aggregation in several *in vitro* systems. This effect may be mediated by the inhibition of phospholipase A₂, which reduces arachadonic acid release from platelet membranes and decreases thromboxane A₂ production.^{44 45} We did not summarise the effects of alcohol on platelet aggregation owing to large differences in assay methods, but if the effects are causal the subsequent impact on reduced risk of coronary heart disease may be substantial.^{46 47}

Although the coefficient of change for several factors was modestly different by sex, few studies were conducted exclusively among women. Decreased first pass metabolism of alcohol among women may accentuate the effects of alcohol on biomarkers of coronary heart disease and thereby reduce the amount of alcohol needed to elicit a response.^{7 48-51} Therefore the projected overall 24.7% reduction in coronary heart disease attributed to the effects of an intake of 30 g of alcohol a day on concentrations of high density lipoprotein cholesterol, fibrinogen, and triglycerides may be achieved at a lower level of intake among women.

Conclusions

A complete review of the risks and benefits of alcohol intake is beyond the scope of this meta-analysis. Although alcohol intake is associated with an increased risk of breast and aerodigestive cancers, and injury,^{7 52} studies on alcohol and mortality suggest that men and women who consume up to 30 g of alcohol a day have the lowest overall risk.^{7-9 11} Should non-drinkers be advised to begin drinking? Criqui has argued⁵³ that most non-drinkers abstain for a reason (for example,

religion, previous health conditions, family history of alcoholism) and therefore should not be advised to start drinking. In agreement with this suggestion current recommendations in the United States and the United Kingdom do not encourage alcohol intake but do state that moderate intake can be part of a healthy lifestyle.^{54 55} Results from our quantitative review suggest that moderate intake is causally related to lower risk of coronary heart disease through alcohol induced changes in lipids and haemostatic factors.

Contributors: EBR wrote the paper. EBR and KF conducted the search and abstracted the data for the analysis. EBR and PW performed the statistical analysis. MC and MJS reviewed and edited the paper and provided input into the design and analysis for the study. EBR and MJS will act as guarantors for the paper.

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