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The cardioprotective association of average alcohol consumption and ischaemic heart disease: a systematic review and meta-analysis

Michael Roerecke, M.Sc.^{1,2} and Jürgen Rehm, Ph.D.^{1,2,3}

¹Centre for Addiction and Mental Health, Toronto, Canada

²Dalla Lana School of Public Health, University of Toronto, Toronto, Canada

³Technische Universität Dresden, Dresden, Germany

Abstract

Aims—Most but not all epidemiological studies suggest a cardioprotective association for low to moderate average alcohol consumption. The objective was to quantify the dose-response relationship between average alcohol consumption and ischaemic heart disease (IHD) stratified by sex and IHD end point (mortality vs. morbidity).

Methods—A systematic search of published studies using electronic databases (1980–2010) identified 44 observational studies (case-control or cohort) reporting a relative risk measure for average alcohol intake in relation to IHD risk. Generalized least-squares trend models were used to derive the best-fitting dose-response curves in stratified continuous meta-analyses. Categorical meta-analyses were used to verify uncertainty for low to moderate levels of consumption in comparison to long-term abstainers.

Results—The analyses used 38,627 IHD events (mortality or morbidity) among 957,684 participants. Differential risk curves were found by sex and end point. Although some form of a cardioprotective association was confirmed in all strata, substantial heterogeneity across studies remained unexplained and confidence intervals were relatively wide, in particular for average consumption of 1–2 drinks/day.

Conclusions—A cardioprotective association between alcohol use and ischaemic heart disease cannot be assumed for all drinkers, even at low levels of intake. More evidence on the overall benefit-risk ratio of average alcohol consumption in relation to ischaemic heart disease and other diseases is needed in order to inform the general public or physicians about safe or low-risk drinking levels.

Keywords

alcohol drinking; alcoholic beverages; case-control studies; cohort studies; coronary artery disease; coronary disease; meta-analysis

Corresponding author: Michael Roerecke, Research Analyst, Section Public Health and Regulatory Policies, Centre for Addiction and Mental Health, 33 Russell Street, Room T425, Toronto, Ontario, Canada M5S 2S1, Tel: ++001 416 535 8501 ext. 6907, Fax: ++001 416 260 4156, m.roerecke@web.de.

Co-author:

Jürgen Rehm, PhD, Professor and Chair, Addiction Policy, Dalla Lana School of Public Health, University of Toronto, Canada, Director, Social and Epidemiological Research Department, Centre for Addiction and Mental Health, Toronto, Ontario, Canada, Professor, Dept. of Psychiatry, Faculty of Medicine, University of Toronto, Canada, Head, Epidemiological Research Unit, Technische Universität Dresden, Klinische Psychologie & Psychotherapie, jtrehm@aol.com

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INTRODUCTION

The health effects of alcohol consumption are manifold, some beneficial, but most detrimental. While the influence on injuries, whether intentional or unintentional, and on several cancers has been shown to be negative with substantial public health impact, the effect on some health outcomes, such as ischaemic stroke, possibly diabetes, but most strongly ischaemic heart disease (IHD), seems to be beneficial when drinking is not heavy on average (1). Many drinkers cite health benefits, mostly for cardioprotection, as a reason for drinking alcohol (2), despite often raised concern in the scientific literature about the causality of a cardioprotective effect.

Oftentimes referred to as a J-shaped curve, several meta-analyses of observational studies seem to show relatively strong evidence for a cardioprotective association of average alcohol intake on IHD risk (3–6). However, there has been a consistent debate on the limitations of current observational evidence, much of which relates to questions of exposure assessment (7–9), the choice of the reference group (sick-quitter effect) (10, 11), and residual confounding and/or over-adjustment for intermediate risk factors for IHD (1, 12–14). These limitations make clinical and public health recommendations for low levels almost impossible at this point, and concern about assuming a causal relationship between alcohol consumption and IHD incidence seems to be well justified.

The risk curve seems to decline sharply with a slow turn up with higher average alcohol consumption. The two most recent meta-analyses showed that a detrimental risk for heart disease is not reached until average consumption exceeds 72 g/day (3) and > 60 g/day (6). The lowest consumption levels are of particular interest because this sharply declining risk curve suggests that cardioprotection is already achieved at very low doses of alcohol intake and the risk of other diseases shows a strong positive and linear association with increasing alcohol intake. However, results from meta-analyses suggest that the risk from average alcohol consumption is differential for men and women, and for the investigated heart health outcome (mortality versus morbidity). Furthermore, the shape of the risk curve has been shown to depend on the reference group, that is, whether the comparison group comprised current non-drinkers or long-term abstainers. Thus, relative risk estimates of low or moderate drinkers are typically biased, depending on which reference group was used.

Ronksley et al. focused on the question of whether any alcohol consumption is beneficial compared with non-drinkers (6). While they found strong evidence for a protective effect of alcohol consumption on several heart disease outcomes, they did not stratify average alcohol consumption by sex, or report the risk of IHD by levels of alcohol consumption in relation to long-term abstainers. They reported a pooled statistically significant protective effect for both mortality and incidence for up to 60 g/day in comparison to current non-drinkers at baseline, thus ignoring the effect of former drinkers.

In this meta-analysis we used strict inclusion criteria to identify high quality observational studies reporting analyses stratified by sex and end point suitable for an investigation of a curvilinear relationship (i.e., identification of a cardioprotective or detrimental association at different levels of alcohol intake), as well as consideration of bias in reported effect estimates because of differentially defined reference groups. Furthermore, we conducted meta-analyses using a categorical approach in addition to a continuous dose-response approach, thus reflecting a more realistic assessment of uncertainty around the curvilinear relationship, in particular at low levels of alcohol intake.

METHODS

Search strategy

This meta-analysis followed the guidelines set by the MOOSE statement (15). We systematically searched the following electronic databases from January 1980 to the second week of April 2010: MEDLINE, EMBASE, Web of Science (Science Citation Index Expanded, Social Sciences Citation Index, Arts & Humanities Citation Index). In addition we scrutinized relevant reviews (16–24), meta-analyses (3, 25–29), and references of identified papers. Excluding letters, editorials, conference abstracts, reviews, and comments, the following free-text keywords and subject headings were used to identify relevant articles in electronic databases: (alcohol drinking OR alcoholic beverages OR beverages OR (alcohol AND (drinking or intake or consumption) OR (ethanol AND drinking or intake or consumption)) AND (myocardial ischemia OR myocardial infarct* OR coronary disease OR heart diseases OR coronary artery disease OR coronary heart disease OR angina OR cardiac death* OR ischaemic heart disease OR ischaemic heart disease OR cardiac event* OR coronary event*) AND (cohort studies OR epidemiologic studies OR follow-up studies OR longitudinal studies OR prospective studies OR case-control studies OR retrospective studies) AND (ratio* OR risk*). No language restrictions were applied. Inclusion criteria were: 1) case-control or cohort study, 2) a measure of risk and its corresponding measure of variability was reported (or sufficient data to calculate these), 3) IHD analyzed as a separate outcome (ICD-9: 410–414, ICD-10: I20–25), 4) exposure measurement had to: (a) have at least three categories of alcohol consumption reported among current drinkers to allow for finding a curvilinear relationship, (b) cover a reference period of more than 2 weeks for average alcohol consumption at baseline (or before incident case for case-control studies), (c) average consumption had to be determined by at least a combination of usual frequency and usual volume or the number of drinks in the specified reference period, 5) estimates were at least age-adjusted.

Because the focus of this meta-analysis was epidemiologic quality of selected studies, including measurement of alcohol consumption, we excluded studies where a semi-quantitative food frequency questionnaire with an ambiguous combination of frequency and volume in a single question was used to assess average consumption, as well as qualitative characterizations of alcohol exposure, such as “problem drinkers” or “social drinkers”. Self-reported IHD morbidity, or cardiovascular outcomes combined (i.e., including stroke), and samples containing only high risk populations were also excluded. We preferred estimates stratified by sex, endpoint (morbidity and mortality), and race (black and white). Where possible, we avoided estimates that were adjusted for blood pressure or cholesterol level or treatment/history for these conditions because these represent mediators rather than confounders in the relationship between alcohol consumption and IHD (30, 31), but accepted these if other estimates were not available. One author performed the search and excluded studies at the first exclusion pass based on title and abstract. Studies identified for a more detailed assessment were discussed and agreed upon by both authors without blinding of study characteristics.

Data extraction and synthesis

We abstracted information on RR estimates and their corresponding variances, number of cases and controls or persons at risk for each reported category of average alcohol intake (if not directly reported, we estimated these based on standard formulas) (32, 33), study design, end point, sex, country, age at baseline, length of follow-up, first year of baseline assessment, and specific adjustment for covariates. We converted alcohol intake into g/day using the midpoints (mean) of reported categories. For open-ended categories we added $\frac{3}{4}$ of the previous category to the lower bound. We used reported conversion factors when

standard drinks were the unit of measurement, or standard conversion factors (34). If necessary, multiple reported analyses per stratum were combined using fixed-effects models, so that each article contributed at most one dose-response curve per stratum(35). If the reference category was not a corresponding abstainer group but, for example light drinkers, we re-calculated the effect size measure to reflect abstainers as the reference category. Former drinkers were excluded from all analyses; when current non-drinkers were the reference group, we adjusted mortality estimates for the effect of former drinking compared to lifetime abstention based on a previous meta-analysis (36) to avoid the sick-quitter effect. Based on a previous meta-analysis on former drinking compared with lifetime abstainer were used to correct the RRs of current drinkers in primary studies in our analysis where current non-drinkers were the reference group (i.e., the reference group included former drinkers). In men, a pooled RR = 1.25 was multiplied by the mean fraction of former drinkers among all current non-drinkers (0.32) and added to the respective RRs of current drinking groups from primary studies used in our analysis when current non-drinking was the reference group. In women, the correction factors were RR = 1.54 with 0.08 fraction former drinkers among all current non-drinkers (36). These corrections were done on the log scale. The analyses with morbidity as the health outcome were not adjusted because the risk of former drinking was not statistically significant from that of lifetime abstainers. Those consuming > 72 g/day were excluded from all analyses because of scarcity of data.

Statistical analysis

Hazard ratios, relative risks and odds ratios were treated as measures of relative risk. Expecting a curvilinear relationship between alcohol and IHD risk, we used fractional polynomials (37) to derive the best fitting function for average alcohol consumption in g/day within each stratum of end point and sex using the 'pool-first' approach described by Greenland and Longnecker (35) and Orsini et al. (38). Linear, first- and second-degree models were estimated using the following range of powers for the fractional polynomial meta-analysis: -2, -1, 0, 1, 2, 3 (37). Significant gain in deviance by first- and second-order models was determined by likelihood ratio tests with 1 and 2 degrees of freedom, respectively. Goodness-of-fit statistics were used to choose the best-fitting model (39) with one turning point to avoid local maxima or minima. Many functional forms can be estimated with this approach, among those J-, L-, and U-shaped functions. We investigated sources of heterogeneity across studies in meta-regression models (40–42). A significant effect modification was determined by a likelihood ratio test with 2 d. f. and sub-group analyses were conducted in these cases. Study characteristics included in these interaction analyses were: age at time of IHD event (<65 years, ≥ 65 years), dummy variables for age-only adjustment, and adjustment for blood pressure or cholesterol in reported relative risk estimates. We further tested the impact of study design (cohort vs. case-control) on the results of the analysis involving morbidity in men, which was the only stratum where this was possible due to the number of primary case-control studies.

For the categorical analysis, alcohol intake was classified as follows: 1) lifetime abstainer, 2) occasional drinker (less than weekly drinking or 0.1–2.49 g/day), 3) average amount of alcohol consumed during the reference period (categorization 2.5–11.99 g/day, 12–23.99, 24–35.99). The classification of average alcohol intake corresponds to about 1 standard drink (12g pure alcohol content) (34). When more than one estimate from primary studies was assigned to these categories, we pooled those using fixed-effects and then pooled across studies using DerSimonian-Laird random-effect models to account for between-study heterogeneity (43). We quantified between-study heterogeneity using Cochrane's Q (44) and the I^2 statistic (45). I^2 can be interpreted as the proportion of the total variation in the estimated slopes for each study that is due to heterogeneity between studies. Potential publication bias was examined using Peter's regression-based test (46), and sensitivity

analyses for the influence of single studies on the pooled relative risk were conducted. All meta-analytical analyses were conducted on the natural log scale in Stata statistical software, version 10.1 (47), and $P < .05$ (two-sided) was considered statistically significant.

RESULTS

Out of 1,538 unique citations identified in the search, 392 full papers were retrieved and scanned for inclusion (Figure 1). After removal of studies because of exclusion criteria and duplicate analyses, we selected 44 unique articles for our quantitative analysis (Table 1).

A total of 9,846 IHD events with 13,199 controls among case-control studies, and 6,942 IHD events with end points combined (mortality or morbidity) and 21,839 IHD events stratified by end point among 934,639 persons at risk among cohort studies contributed to this analysis. The number of cases per study ranged from 34 to 6,135, and the total sample size from 309 to 245,207. The majority of selected articles originated in the US ($n = 16$), Japan ($n = 5$), and the UK ($n = 4$), but a wide range of countries were included (Table 1). Only two studies (48, 49) provided stratified estimates for race other than white. We therefore refrained from analyzing those separately and included each estimate into the respective sex and endpoint strata.

Among the articles selected for a quantitative analysis (Table 1), 20 articles reported only estimates for endpoint or sex combined. These estimates were used in any of the respective analyses labeled as 'combined' (Table 3 and 4, Figure 3), whereas 24 articles reporting sex- and endpoint-specific estimates were used in our main analyses.

Continuous dose-response meta-analysis

Figure 2 shows derived continuous dose-response curves for IHD mortality and morbidity stratified by sex. In men, the risk function follows a J-curve with a nadir (lowest point of the curve, i.e., lowest IHD risk) at 31 g/day for IHD mortality (Figure 2a). The reversion point, where no statistical evidence for a cardioprotective effect exists, was reached at 63 g/day. Regarding morbidity in men, a declining curve leveled off for stratified only estimates (Figure 2b) with the nadir at 69 g/day. Analyses using estimates that combined sex or end point (Figures 3a, b), showed similar curves and nadirs. In women a steep J-curve was observed for IHD mortality and morbidity (Figures 2c, d). The nadir and reversion points were substantially lower for both IHD mortality and morbidity in women (11 g/day and 14 g/day, respectively) compared with men. In both sexes, heterogeneity was substantial and highly statistically significant in most models, with I^2 between 46 and 59% (Table 3).

Categorical meta-analysis

The categorical analysis (Table 2) shows the relationship between average alcohol intake and risk of IHD for 1, 2, and 3 standard drinks in comparison to lifetime abstainers. Although the general form of the dose-response relationship derived from the fractional polynomial analyses was confirmed in each stratum, confidence intervals were markedly wider, in particular for 1 or 2 drinks on average. For male mortality, a statistically significant cardioprotective association was detected for 3 standard drinks (RR = 0.78, 95% CI: 0.63–0.97), but not for 1 or 2 drinks of average alcohol consumption (RR = 0.89, 95% CI: 0.79–1.00 for 1 drink/day and RR = 0.86, 95% CI: 0.73–1.02 for 2 drinks/day, Table 2). Except for the category with 3 drinks/day, a statistically significant cardioprotective association was found for male morbidity, regardless of whether only stratified estimates were used (Table 2) or also estimates using combined sex or end points (Table 4); however, there were only 3 studies available for a fully stratified analysis for 3 drinks of average alcohol intake. In women, using only completely stratified studies, a statistically significant

association was found only for up to 1 standard drink on average for mortality, and for up to 2 drinks considering IHD morbidity. The number of studies reporting drinking levels of 3 or more drinks/day on average was very low ($n = 3$).

Only one of the models displayed in Table 2 and 4 showed evidence of publication bias. Sensitivity analyses omitting studies one by one and re-estimating the pooled RR did not reveal any substantial influence of a particular study on the pooled effect estimates. Heterogeneity across studies was substantial in most analyses and highly statistically significant in all continuous dose-response curve models (Table 3) and most categorical models (Table 2 and 4). This was in part expected due to different study design and populations under study; however, power was relatively low in any attempts to identify sources of this heterogeneity. None of the interaction terms investigated were significant, except for age at the time of the IHD event (<65 years, 65 years of age) in women for IHD mortality (sub-group analyses presented in Table 5). We found no evidence for a study design effect in the analysis with IHD morbidity as the outcome measure in men (likelihood ratio test $p = 0.57$, 2 d. f.).

DISCUSSION

Many epidemiological studies have reported a cardioprotective association for low to moderate alcohol intake in the last three decades; however, the number of published studies alone certainly is not an indicator of the strength of the evidence for a cardioprotective association, let alone a causal effect. This meta-analysis separated former drinkers from the reference group and presents the respective risk curves for average alcohol consumption stratified by sex and IHD endpoint with lifetime abstainers as the comparison group. The results indicate that, given current epidemiological evidence, some form of a cardioprotective association seems plausible for both sexes and end points.

The strength of the cardioprotective association, at low levels of average alcohol consumption in particular, differed by sex and outcome. Furthermore, the upturn of the risk function, indicating a turn into a detrimental association, was differential by sex and outcome. With regard to the difference in risk curves for mortality and morbidity, one potential explanation might be the younger age at the time of the event in morbidity studies. Although the difference is relatively small, risk curves are typically attenuated with increasing age because age is one of the strongest risk factors for chronic diseases (50). Regarding levels of average alcohol consumption, in analyses completely stratified by sex and end point, we detected less cardioprotection for mortality as an outcome compared to previous meta-analyses, in particular for low levels of alcohol intake (1–2 drinks per day). The exception was morbidity in women, which showed stronger effects compared with other meta-analyses, but relatively few studies were available for such an evaluation. The risk estimates for current occasional drinkers did not reach statistical significance (comparable to those by Ronksley et al. (6)), nor was the potential cardioprotective association substantial. However, the difference for IHD endpoints was already apparent at such low consumption levels with stronger protective effects for morbidity outcomes.

The shape of the risk curves in each stratum supports a cardioprotective association. However, although we stratified by sex and end point and focused on the quality of exposure and outcome assessment, except for mortality in women, all models showed substantial unexplained heterogeneity, which makes it likely that more factors play a substantial role than we were able to incorporate in our analysis. This heterogeneity is better reflected in CIs from the categorical analysis because it takes into account all data points in a given category, unlike the CIs from the continuous dose-response analysis, which were derived from the functional form and the distance from the origin (0 g/day alcohol and lifetime

abstention). CIs from the continuous analysis thus overestimate precision around the curves at low levels of consumption (1–3 drinks on average per day), as we have shown. Considering the categorical meta-analysis, evidence of a cardioprotective association for IHD mortality among both sexes was borderline for 1–3 drinks/day as upper confidence limits for pooled relative risk estimates were close to or above 1, indicating no statistically difference in IHD risk compared to lifetime abstainer.

Limitations

Several limitations apply to this analysis. Although results were robust in several sensitivity analyses examining study-specific aspects including assessment of adjustment for several IHD risk factors, we cannot exclude the possibility of residual confounding because our meta-analysis was subject to bias, which might be present in the primary studies. Potential residual confounding could bias the results in both ways, a more pronounced cardioprotective effect or a less pronounced effect. We did, however, include many quality characteristics in our eligibility criteria, stratified by sex and end point, adjusted for the sick-quitter effect, and used individual study characteristics in meta-regression models to examine detected heterogeneity across studies. Nevertheless, although we used strict inclusion and exclusion criteria, these were not optimal from a pure evidence point of view. For example, strict control for smoking, health status at baseline, or longer reference periods for alcohol assessment could be important factors to consider, but would have resulted in very few studies for analysis. Thus, our inclusion and exclusion criteria were somewhat driven by practicality. The list of confounders adjusted for in the individual studies varied widely, and a substantial number only included age (sometimes to avoid inclusion of blood pressure or cholesterol level as intermediate factors). However, confounding other than age on the alcohol-heart relationship seems to be usually small (6). Our results were confirmed when only studies were considered that did not adjust for intermediate factors, such as blood pressure or cholesterol level. Problems of residual confounding apply equally to all other risk factors for IHD examined in observational studies. Many risk factors for IHD have been identified, of which many potentially interact with alcohol, enhancing or diminishing the effect of alcohol. However, the number of cases in cohort studies is usually too small to thoroughly investigate such interaction effects. Nevertheless, alcohol is one of the most investigated dietary risk factors for IHD (51).

Although self-reported alcohol consumption seems to be reasonably valid (8, 52), some drinking and non-drinking groups change their alcohol consumption over time (53, 54). Thus, all drinking groups we have identified were subject to misclassification bias. It should be noted that sensitivity analyses investigating potential effect modification by study characteristics were subject to low power because of the small number of studies in several subgroups. Furthermore, we cannot derive meaningful conclusions on the shape of the curve beyond 72 g/day because of scarcity of data.

Implications

Based on our meta-analysis, some form of a cardioprotective association for IHD morbidity and mortality is hard to deny given epidemiological evidence. However, one needs to consider sex and a specific endpoint as a reference point for any risk-benefit relationship. An important issue at low levels of alcohol intake, where a cardioprotective effect can be a substantial part of the overall risk-benefit relationship (28). While the nadir (maximum cardioprotective association) for mortality and morbidity in men was located at average intake between 33 and 69 g/day, showing a significant effect in both the fractional polynomial and categorical analysis, these levels are by no means safe from a clinical and public health perspective as they have been shown to be detrimentally associated with many other disease outcomes (55). However, for low average intake, such as 1 to 2 drinks per day,

we have shown that a cardioprotective association cannot be readily assumed for all populations at such drinking levels. Attenuation of IHD risk with higher age at the time of the event in women for IHD mortality in our study warrants caution in assuming the cardioprotective effect is most important or pronounced in the elderly because of higher prevalence of IHD. Nevertheless, the low number of studies to investigate this issue warrants cautious interpretation.

A substantial part of the unexplained heterogeneity might have been caused by irregular heavy drinking occasions, which we were unable to investigate in this report. A previous meta-analysis found a relative risk of 1.45 (95% CI: 1.24–1.70) for participants with such drinking occasions vs. no such drinking occasions, excluding abstainers, former drinkers where possible, occasional drinkers, and regular heavy drinkers (29). Other effect modifiers are certainly plausible. However, given the shape of the derived function, if a strong effect modification by study characteristics would be found, the curve would be divided into a stronger cardioprotective association and an attenuated one. This means that identification of a strong effect modifier would also identify a group with stronger cardioprotection compared to our results, given no bias due to other factors occurred. Nevertheless, heterogeneity suggests that a potential cardioprotective association cannot be generally assumed, even at low levels of intake. The reasons for this heterogeneity of effect need to be investigated before alcohol consumption for health reasons can be advocated in general. Moreover, for any particular individual, the alcohol-IHD relationship cannot be seen in isolation from other disease outcomes because even at low levels of alcohol intake the effect on many other disease outcomes is detrimental (1, 56).

Physicians are faced with numerous problems regarding advice on alcohol intake for individual patients because of the complex potentially beneficial or detrimental effects of alcohol on IHD, although patients seem to be open to advice on change of alcohol consumption from their physician (57). Due to ethical and logistical reasons resulting in a lack of long-term randomized trials providing important experimental evidence, it is of utmost importance to carefully examine the available epidemiological evidence. Regarding causality of effects, a potential cardioprotective association is supported by short-term experimental evidence on surrogate biomarkers, such as increasing HDL cholesterol, reducing fibrinogen levels, and inhibition of platelet activation (58–60). Indeed, this might be the strongest argument for causality given that observational findings are always prone to residual confounding and bias due to study design.

Forming clinical advice for individuals to start drinking for health purposes based on epidemiological evidence alone cannot be advocated here because too many questions on confounding or effect modification from other heart disease risk factors, such as education, income, physical activity, or smoking cannot be accurately answered at this time (12, 61, 62). Substantial heterogeneity even at low levels of alcohol intake we found in our analysis strengthens this conclusion. One or two drinks per day of averaged intake should not be seen as a safe level of drinking because problem drinking behaviour, which is not limited to a specific average daily alcohol intake, can already be seen at these levels (63). It seems that neither taking up drinking because of health reasons, nor abstinence for low level drinkers who have shown themselves able to control their drinking should be promoted. Moreover, the number of drinkers with 1 or 2 drinks per day as a steady daily amount of drinking have shown to be very small even in populations with overall low abstention rates (64).

Findings from this study support current low-risk drinking guidelines, if these recognize lower drinking limits for women. If one only takes into account average volume, this study showed that most of the cardioprotective effect can be already achieved with 1–2 drinks/day for men and 1 drink/day for women. Higher average consumption should be discouraged

because of the negative effects on many other disease outcomes (1). Furthermore, very low consumption levels, such as below 1–2 drinks per week do not seem to confer substantial cardioprotective effects. However, at the same time it seems that this does not apply to all drinkers and that other determinants of the alcohol effect on heart disease that were not captured by average consumption as an exposure measurement, such as drinking patterns (29), might play an important role. Given the negative impact of heavy drinking occasions on heart disease and injuries (1), low-risk drinking guidelines should also include limits of drinks per occasion.

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Abbreviations

CI	confidence interval
IHD	ischaemic heart disease
RR	relative risk

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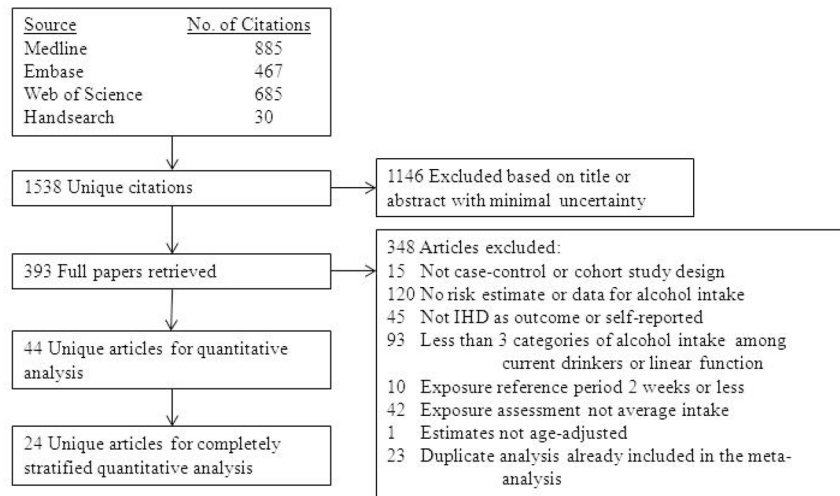
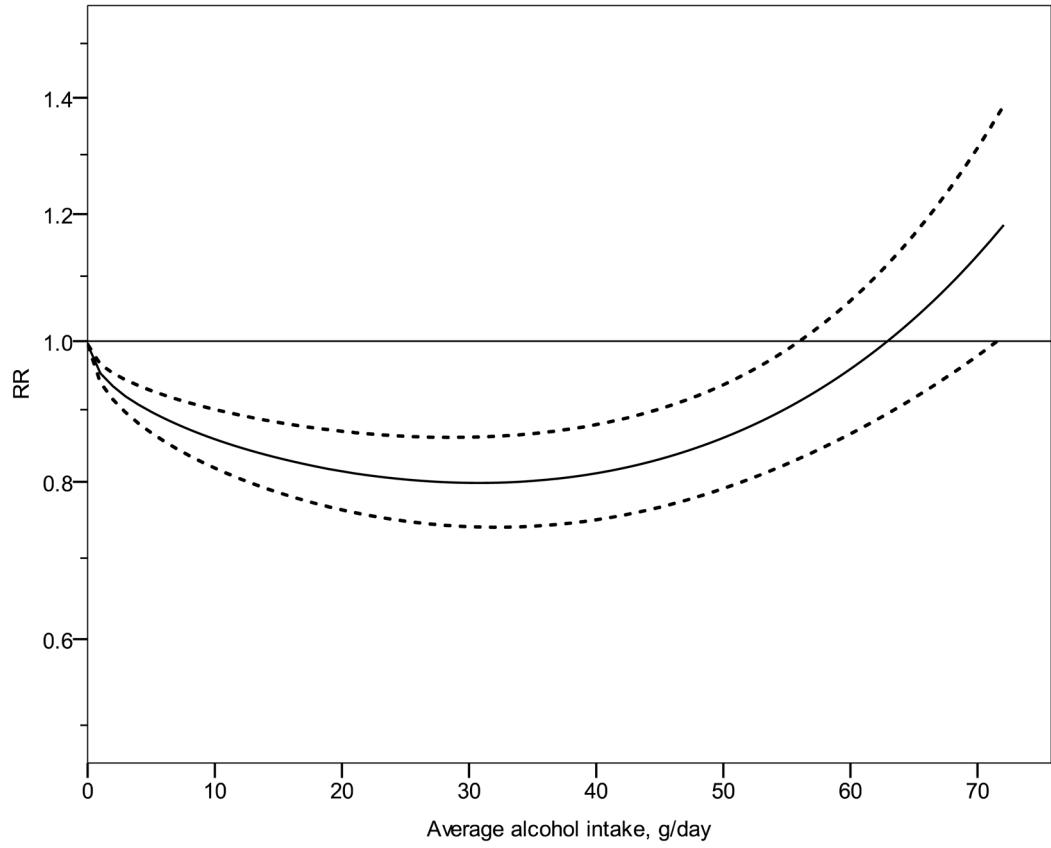


Figure 1.
Study selection process

Figure 2a.

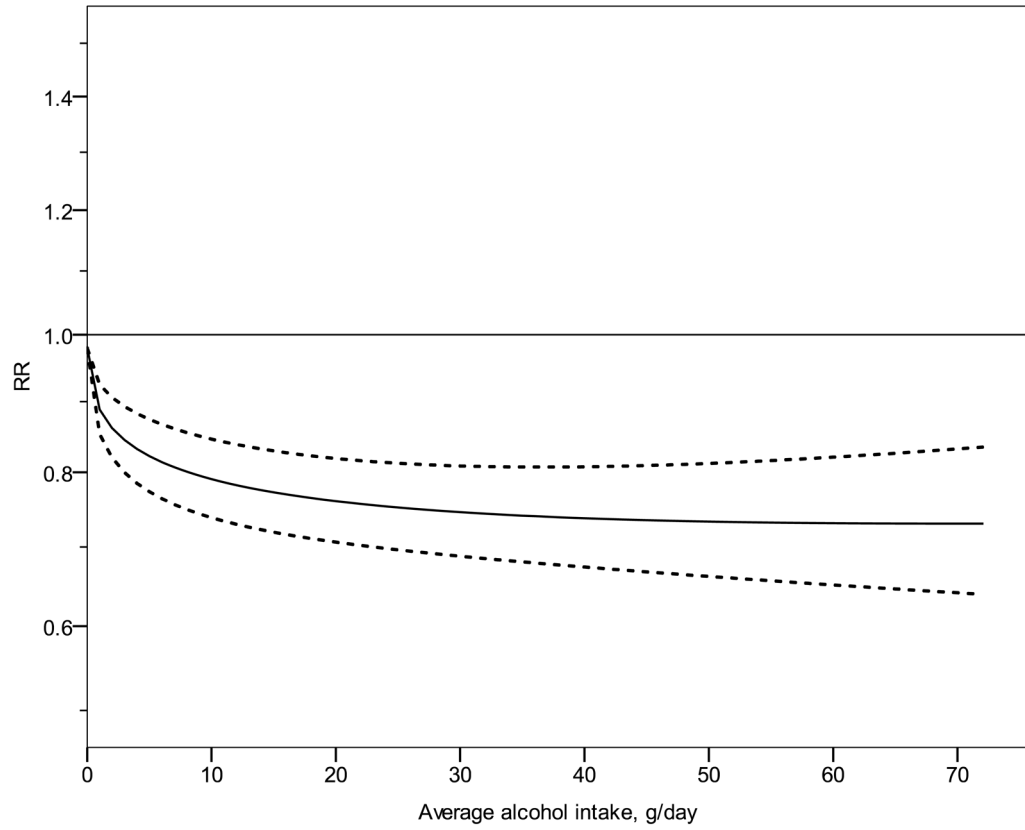


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Figure 2b.

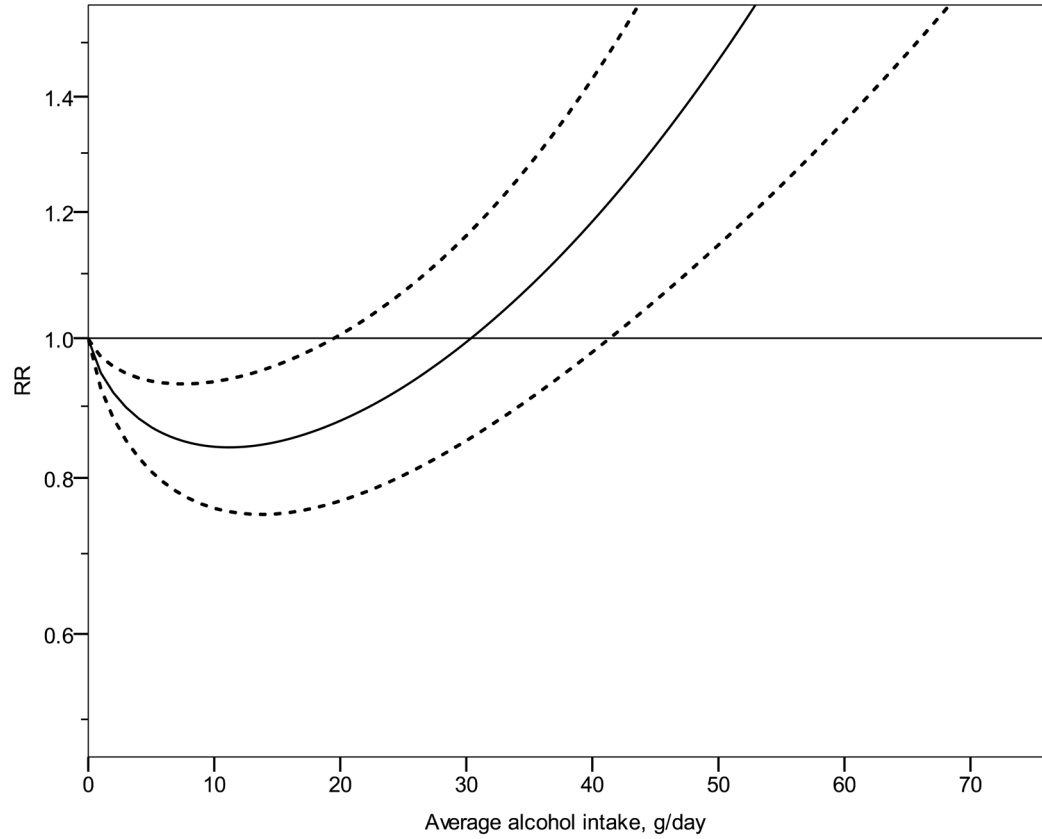


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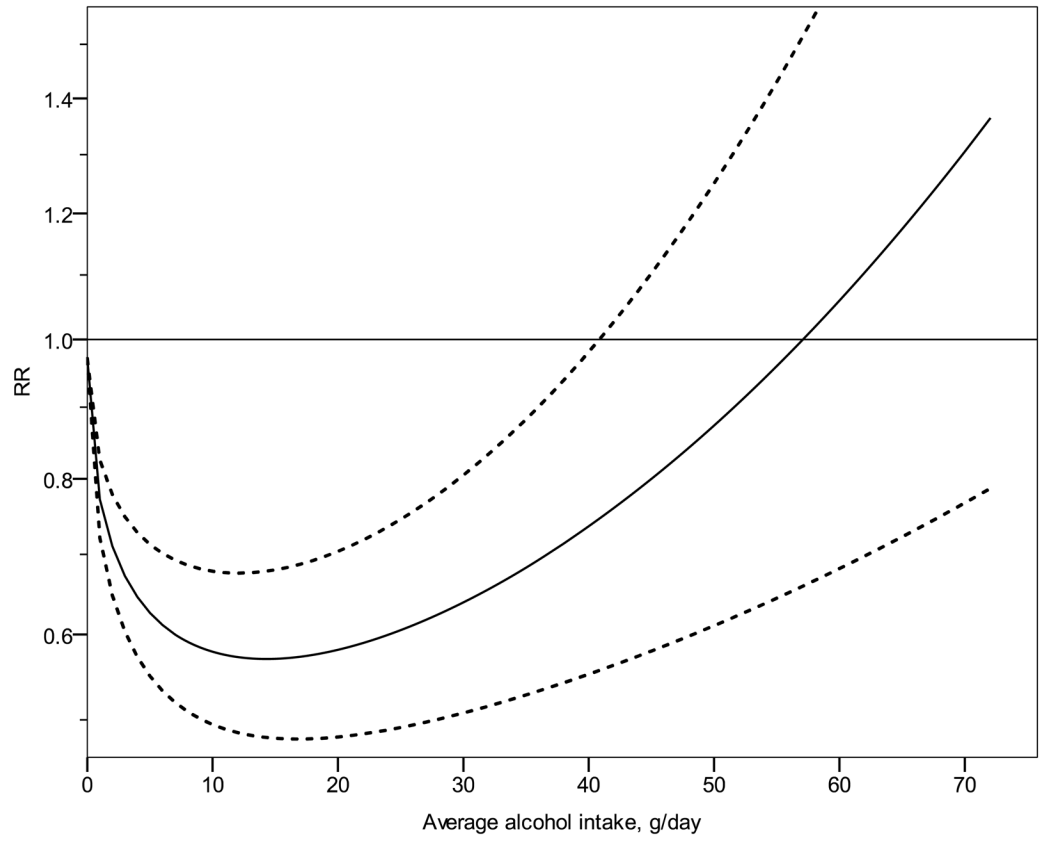
Figure 2c.



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Figure 2d.**Figure 2.**

Relative risk functions (solid lines, on the natural log scale) and corresponding 95% confidence intervals (dashed lines) for the dose-response relationship between average alcohol intake and risk of ischaemic heart disease (IHD), using only studies completely stratified by sex and endpoint, 1980–2010. 2a) IHD mortality in men, 2b) IHD morbidity in men, 2c) IHD mortality in women, 2d) IHD morbidity in women

Figure 3a.

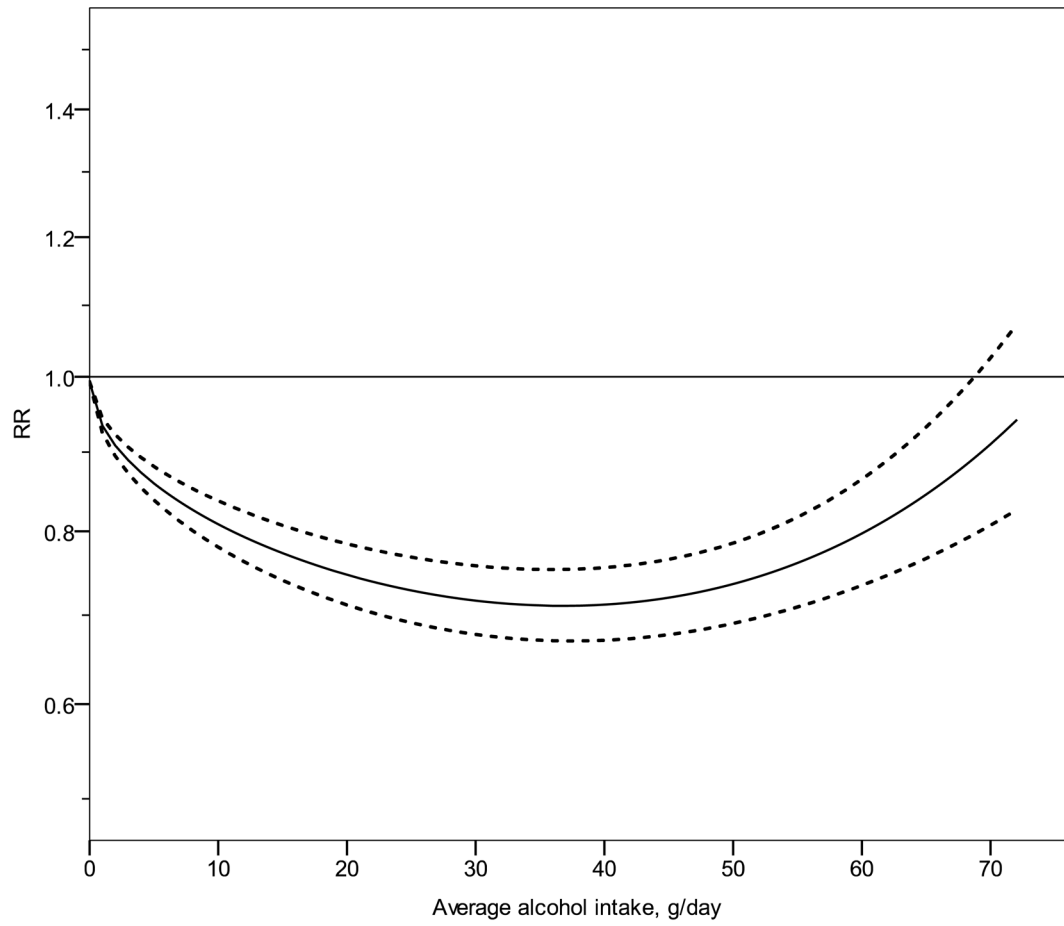


Figure 3b.

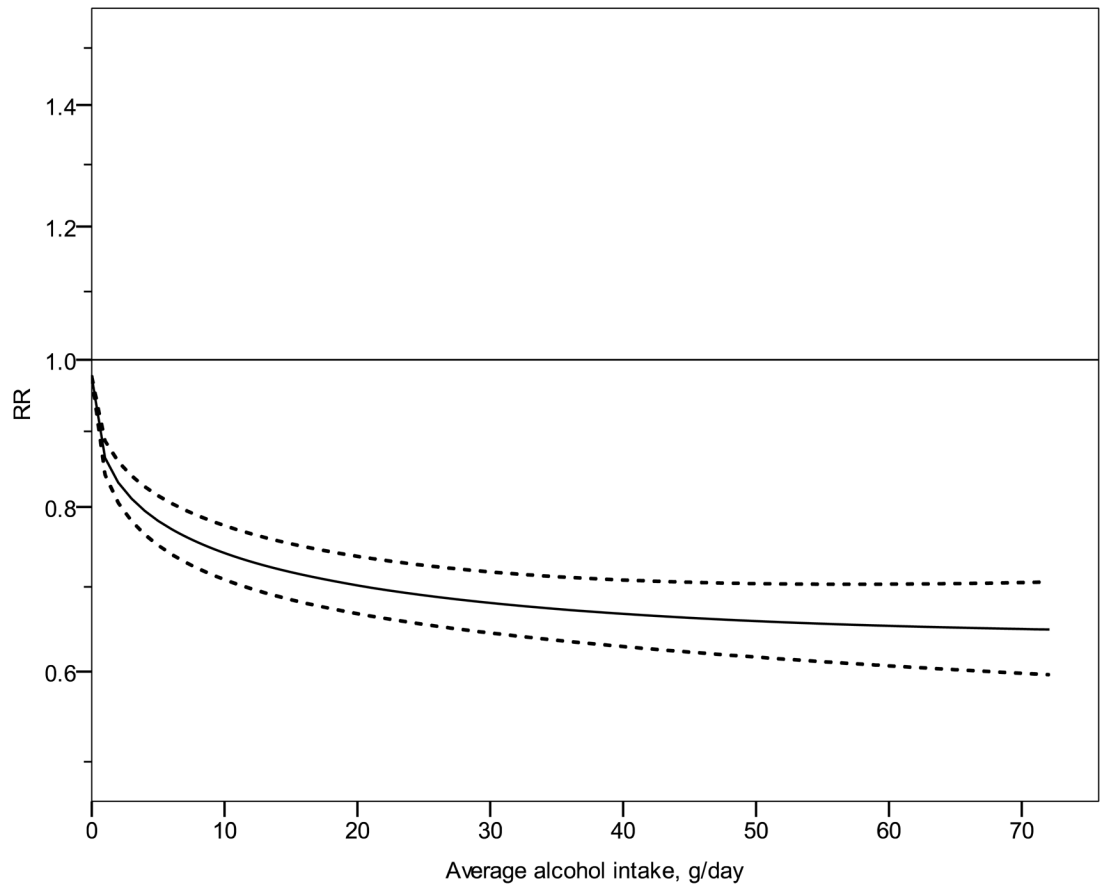
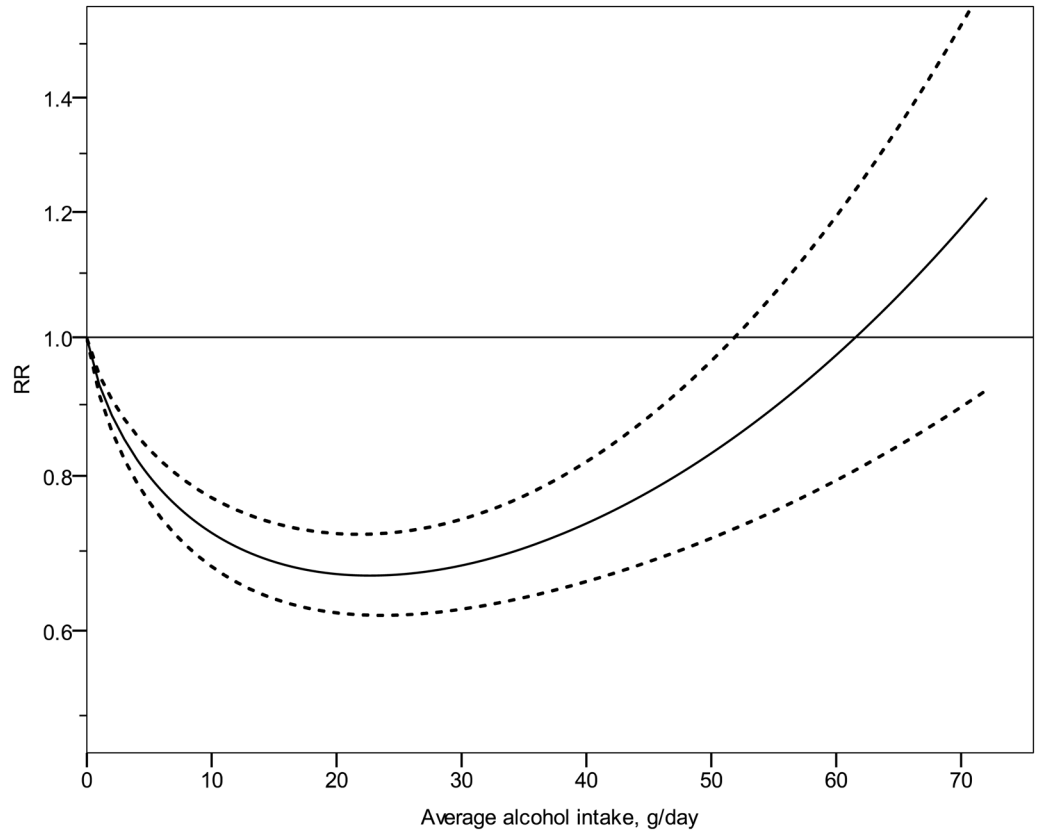


Figure 3c.



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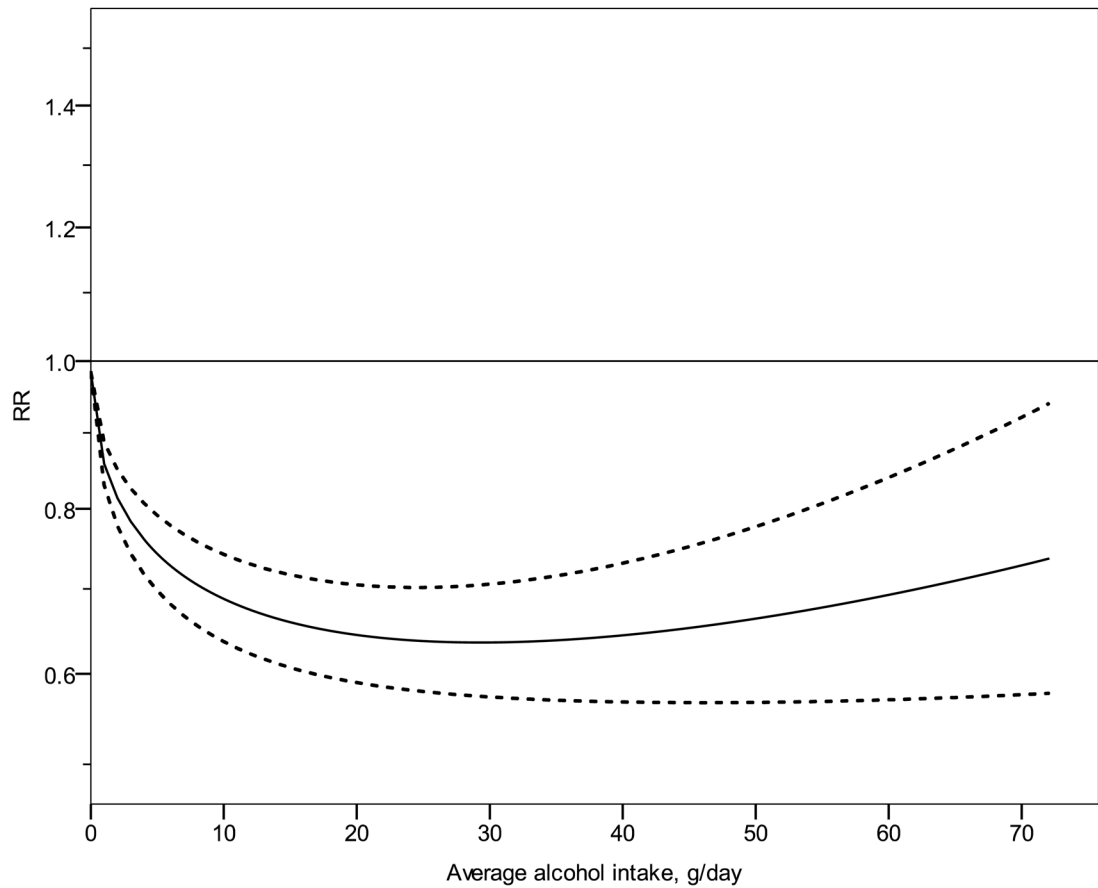
Figure 3d.

Figure 3. Relative risk functions (solid lines, on the natural log scale) and corresponding 95% confidence intervals (dashed lines) for the dose-response relationship between average alcohol intake and risk of ischaemic heart disease (IHD), using also studies with combined sex or endpoint, 1980–2010. 3a) IHD mortality in men, 3b) IHD morbidity in men, 3c) IHD mortality in women, 3d) IHD morbidity in women

Table 1

Characteristics of 43 studies selected for quantitative analysis of the association between average alcohol consumption and risk of ischaemic heart disease, 1980–2010

Study	Provided at least one stratified data set	End Point	Sex	Study Design	No. of Cases	Total Sample Size, No.	Country	Adjustment
Dyer et al. (65) 1980	Yes	Mortality	M	Cohort	149	1832	US	Age, diastolic BP, smoking, serum cholesterol
Kagan et al. (66) 1981	Yes	Morbidity	M	Cohort	113	7591	US	Age
Gordon et al. (67) 1983	Yes	Mortality	W, M	Cohort	906	4625	US	Age, systolic BP, smoking, relative weight, Sf 0–20, Sf 20–400 lipoproteins
Kaufman et al. (68) 1985	Yes	Morbidity	M	Case-control	1095	1596	US	Age, smoking
Colditz et al. (69) 1985	No	Mortality	Combined	Cohort	42	1161	US	Age
Camacho et al. (70) 1987	Yes	Mortality	W, M	Cohort	421	4590	US	65 years or older, male, black, disabled, health fair or poor, less than adequate income, less than 12 years schooling, never smoked, relatively inactive, not married, no organization membership, depressed, uncertain
Seragg et al. (71) 1987	Yes	Mortality, Morbidity	W, M	Case-control	594	2321	New Zealand	Age
Kono et al. (72) 1991	No	Morbidity	Combined	Case-control	83	340	Japan	Age, smoking, strenuous exercise, BMI, systemic hypertension, diabetes, parental heart disease, job class
Jackson et al. (73) 1991	Yes	Morbidity	W, M	Case-control	283	1035	New Zealand	Age, smoking, BP, social class, exercise, recent change in drinking
Goldberg et al. (74) 1994	Yes	Mortality	M	Cohort	132	3793	US	Age, systolic BP, serum cholesterol, serum triglycerides, serum uric acid, smoking, coffee intake, total caloric intake
Doll et al. (75) 1994	Yes	Mortality	M	Cohort	1100	10 604	UK	Age, smoking, year of death, history of previous disease
Shaper et al. (76) 1994	Yes	Mortality, morbidity	M	Cohort	512	7729	UK	Age, social class, BMI, smoking
Iso et al. (77) 1995	No	Combined	M	Cohort	34	2890	Japan	Age

Study	Provided at least one stratified data set	End Point	Sex	Study Design	No. of Cases	Total Sample Size, No.	Country	Adjustment
Rehm et al. (78) 1997	Yes	Combined, mortality, morbidity	W, M	Cohort	2112	6788	US	Age, smoking
McElduff et al. (79) 1997	No	Combined	W, M	Case-control	2483	3964	Australia	Age, smoking, BP, high cholesterol, angina, stroke, previous MI, diabetes
Kitamura et al. (80) 1998	No	Combined	M	Cohort	80	8476	Japan	Age, serum total cholesterol, smoking, BMI, left ventricular hypertrophy, history of diabetes
Maskarinec et al. (81) 1998	Yes	Mortality	W, M	Cohort	1100	27 678	US	Age, race, education, BMI, smoking
Romelsjö et al. (82) 1999	No	Combined	M	Cohort	279	49 618	Sweden	BP (cont.), BMI, father's social class, running away from home, poor schooling wellbeing, parental divorce, poor emotional control, 0-1 friends, unemployment for >3 months during lifetime, poor health, smoking
Hippe et al. (83) 1999	No	Combined	W, M	Cohort	1763	24 664	Denmark	Age, population of origin
Grønbeæk et al. (84) 2000	No	Mortality	Combined	Cohort	1075	19 006	Denmark	Age, sex, smoking, education, physical activity, BMI,
Liao et al. (85) 2000	Yes	Mortality	W, M	Cohort	1378	43 695	US	Age, race, smoking, history of hypertension, diabetes, heart disease, marital status, education, self-perceived health status
Genchev et al. (86) 2001	No	Morbidity	Combined	Case-control	155	309	Bulgaria	Age, sex
Tavani et al. (87) 2001	No	Morbidity	Combined	Case-control	507	985	Italy	Age, sex, education, physical activity, BMI, cholesterol, coffee, smoking, hyperlipidemia, diabetes, hypertension, family history of MI
Sempos et al. (49) 2002	No	Combined	W, M	Cohort	244	1158	US	Age
Romelsjö et al. (88) 2003	Yes	Morbidity	W, M	Case-control	1300	3534	Sweden	Age, hospital, marital status, smoking, physical activity, cardiovascular disease, job strain, social anchorage, life control
Marques-Vidal et al. (89) 2004	Yes	Combined, morbidity	M	Cohort	318	9750	France, Northern Ireland	Age, marital status, education, vigorous exercise, BMI, systolic BP, diastolic BP, total cholesterol, triglycerides (Ln), smoking, anti-hypertensive drug treatment, hypolipidaemic treatment, centre

Study	Provided at least one stratified data set	End Point	Sex	Study Design	No. of Cases	Total Sample Size, No.	Country	Adjustment
Wells et al. (90) 2004	No	Combined	W, M	Case-control	1164	2935	New Zealand	Age
Fuchs et al. (48) 2004	No	Combined	M	Cohort	449	6276	US	Age, smoking, BMI, LDL-level, WHR, education, income, sport index, diabetes
Tavani et al. (91) 2004	Yes	Morbidity	W	Case-control	558	1602	Italy	Age, cohort, education, BMI, smoking, coffee, diabetes, hyperlipidemia, BP, family history of AMI
Mäkelä et al. (92) 2005	No	Combined	W, M	Cohort	854	6392	Finland	Age, cohort period, marital status, education, smoking
Kabagambe et al. (93) 2005	No	Morbidity	Combined	Case-control	1465	3234	Costa Rica	Age, smoking
Mukamal et al. (94) 2006	No	Combined	Combined	Cohort	675	4410	US	Age, race, sex, education, marital status, smoking, exercise intensity, depression score, frequent aspirin use, BMI, diabetes
Tolstrup et al. (95) 2006	No	Combined	W, M	Cohort	2032	53 500	Denmark	Age, education, smoking, physical activity, BMI, total intake of vegetables, fruits, fish, and saturated fat
Gun et al., (96) 2006	Yes	Mortality	M	Cohort	295	16 547	Australia	Age, calendar period, smoking
Harriss et al. (97) 2007	Yes	Mortality	W, M	Cohort	249	38 248	Australia	Age, country of birth, smoking, total daily energy intake and fruit intake, saturated fat intake
Dom et al. (98) 2007	Yes	Morbidity	W	Case-control	159	1190	US	Age, BMI, education, race, smoking, menopausal status
Henderson et al. (99) 2007	Yes	Mortality	M	Cohort	572	70 739	US	Age
Hart et al. (100) 2008	Yes	Mortality, morbidity	M	Cohort	2534	6000	UK	Age
Ikehara et al. (101) 2008	Yes	Mortality	W, M	Cohort	736	83 682	Japan	Age
Ikehara et al. (102) 2009	Yes	Mortality	M	Cohort	183	18 595	Japan	Age
Bazzano et al. (103) 2009	Yes	Combined, mortality	M	Cohort	1564	64 597	China	Age
Key et al. (104) 2009	No	Mortality	Combined	Cohort	213	47 254	UK	Age, sex, smoking

Study	Provided at least one stratified data set	End Point	Sex	Study Design	No. of Cases	Total Sample Size, No.	Country	Adjustment
Mukamal et al. (105) 2010	No	Mortality	Combined	Cohort	6135	245 207	US	Age, sex, race, smoking, marital status, education, region, urbanization, BMI, general health status
Arriola et al. (106) 2010	No	Combined	W, M	Cohort	532	37 544	Spain	Age, centre, smoking, height, education, physical activity, WHR, vitamin E, antithrombotic and antithrombotic drugs, energy intake

Abbreviations: BMI, body mass index; IHD, ischaemic heart disease; LDL, low density cholesterol level; M, men; W, women; WHR, waist-hip-ratio.

Table 2

Categorical analysis of the association between average alcohol intake and risk of ischaemic heart disease, stratified by sex and end point (n = 24 studies), 1980–2010

Sex	End Point	Average alcohol intake, g/day	No. of Studies	No. of Cases	Total sample size	Relative Risk (95% CI)	P Value for Heterogeneity	I ² , % (95% CI)	P Value for Publication bias	
Men	Mortality	Lifetime abstainer	16	2460	98 797	1.0				
		Occasional ^a	5	248	7376	0.94 (0.74–1.21)	0.18	37 (0–76)	0.90	
	Morbidity	2.5–11.99	17	1792	68 249	0.89 (0.79–1.00)	<0.001	65 (42–79)	0.92	
		12–23.99	12	1113	23 994	0.86 (0.73–1.02)	<0.001	72 (49–84)	0.42	
		24–35.99	11	617	34 821	0.78 (0.63–0.97)	<0.001	76 (58–87)	0.40	
		Lifetime abstainer	9	1644	48 270	1.0				
		Occasional ^a	3	412	3856	0.82 (0.65–1.02)	0.31	15 (0–59)	0.80	
		2.5–11.99	9	1540	14 313	0.77 (0.65–0.92)	0.001	68 (39–83)	0.13	
	Women	Mortality	12–23.99	8	1112	6601	0.75 (0.64–0.88)	0.084	42 (0–73)	0.95
			24–35.99	3	264	2840	0.74 (0.53–1.02)	0.057	65 (0–90)	0.60
Lifetime abstainer			8	1333	72 808	1.0				
Occasional ^a			3	252	8884	0.98 (0.74–1.30)	0.10	58 (0–88)	0.24	
Morbidity		2.5–11.99	8	427	23 569	0.84 (0.74–0.96)	0.24	23 (0–65)	0.81	
		12–23.99	7	75	5442	1.03 (0.84–1.27)	0.40	3 (0–29)	0.01	
		24–35.99	5	37	4188	0.89 (0.57–1.40)	0.10	48 (0–81)	0.57	
		Lifetime abstainer	5	650	2377	1.0				
	Occasional ^a		2	325	1972	0.91 (0.78–1.07)	0.49	0	NA	
		2.5–11.99	5	429	2325	0.54 (0.45–0.65)	0.95	0 (0–44)	0.92	
	12–23.99	5	222	912	0.61 (0.38–0.99)	0.009	70 (25–88)	0.41		
	24–35.99	3	132	421	0.40 (0.14–1.13)	0.002	84 (50–95)	0.25		

Note: Former drinkers were excluded.

^aOccasional = less than 1 drink/week to <2.5 g/day average alcohol intake.

Model-based functional form and key features of the association between average alcohol intake and risk of ischaemic heart disease, by sex and end point, 1980–2010

Table 3

Sex	Stratum	Functional form (x = average alcohol intake, g/day)	No. of Studies	Age at Time of IHD Event, years	Nadir, g/day	Reversion Point, g/day ^a	P Value for Heterogeneity	I ² , % (95% CI)
Stratified only (n = 24 studies)								
Men	Mortality	$\log RR = x^{0.5} + x^3$	17	65	32	63	<0.001	51 (35–63)
	Morbidity	$\log RR = x^{0.5} + \ln(x) * x^{0.5}$	9	63	69	-	0.001	46 (21–63)
Women	Mortality	$\log RR = x + \ln(x) * x$	8	67	11	31	0.014	56 (45–64)
	Morbidity	$\log RR = x^{0.5} + x$	5	63	14	57	<0.001	58 (31–74)
All estimates (n = 44 studies)								
Men	Mortality	$\log RR = x^{0.5} + x^3$	34	57	37	-	<0.001	54 (44–63)
	Morbidity	$\log RR = x^{0.5} + \ln(x) * x^{0.5}$	28	56	72	-	<0.001	46 (32–58)
Women	Mortality	$\log RR = x + \ln(x) * x$	18	58	23	62	<0.001	51 (34–64)
	Morbidity	$\log RR = x^{0.5} + x$	17	63	29	-	<0.001	59 (44–69)

Abbreviations: CI, confidence interval.

^aPoint where the risk function for average alcohol intake turns into a detrimental association with ischaemic heart disease

Table 4

Categorical analysis of the association between average alcohol intake and risk of ischaemic heart disease, by sex and end point^a (n = 44 studies), 1980–2010

Sex	End point	Average alcohol intake, g/day	No. of Studies	No. of Cases	Total sample size	Relative Risk (95% CI)	P Value for Heterogeneity	I ² , % (95% CI)	P Value for Publication bias
Men	Mortality	Lifetime abstainer	34	8347	233 360	1.0			
		Occasional ^b	10	606	8720	0.90 (0.76–1.08)	0.16	32 (0–67)	0.62
	Morbidity	2.5–11.99	34	5006	238 530	0.81 (0.74–0.90)	<0.001	70 (58–79)	0.65
		12–23.99	26	2816	588 135	0.74 (0.66–0.84)	<0.001	68 (53–79)	0.56
		24–35.99	20	1377	45 259	0.74 (0.63–0.86)	<0.001	74 (60–83)	0.26
		Lifetime abstainer	28	3595	60 666	1.0			
		Occasional ^b	9	847	6586	0.87 (0.75–1.01)	0.23	24 (0–64)	0.63
		2.5–11.99	27	4445	74 562	0.77 (0.69–0.86)	<0.001	67 (51–78)	0.61
		12–23.99	22	2852	30 136	0.70 (0.63–0.77)	.006	48 (15–68)	0.99
		24–35.99	16	1231	13 297	0.66 (0.57–0.76)	.004	55 (21–74)	0.89
Women	Mortality	Lifetime abstainer	18	7043	204 285	1.0			
		Occasional ^b	6	410	6731	0.97 (0.84–1.11)	0.34	12 (0–55)	0.19
	Morbidity	2.5–11.99	18	3103	194 512	0.77 (0.70–0.84)	0.037	41 (0–66)	0.77
		12–23.99	15	702	38 696	0.74 (0.60–0.90)	0.002	60 (29–77)	0.61
		24–35.99	10	416	12 575	0.67 (0.56–0.80)	0.15	32 (43–67)	0.67
		Lifetime abstainer	17	2630	21 704	1.0			
		Occasional ^b	6	635	4749	0.92 (0.83–1.02)	0.59	0 (0–64)	0.16
		2.5–11.99	16	2055	31 254	0.70 (0.62–0.78)	0.043	41 (0–68)	0.54
		12–23.99	13	848	13 987	0.69 (0.56–0.84)	<0.001	69 (45–82)	0.57
		24–35.99	11	382	6291	0.62 (0.50–0.77)	0.022	52 (5–76)	0.19

Note: Former drinkers were excluded.

Abbreviations: CI, confidence interval.

^a Combined end point or sex included.

^b Occasional = less than 1 drink/week or <2.5 g/day average alcohol intake.

Table 5

Subgroup analysis for ischaemic heart disease mortality in women (stratified estimates only), 1980–2010

Subgroup	Average alcohol intake, g/day	Studies, No.	Relative Risk (95% CI)	P Value for Heterogeneity	I ² , % (95% CI)
Age at time of event < 65 years					
	Lifetime abstainer	4	1.00		
	2.5–11.99	4	0.78 (0.60–1.00)	0.47	0 (0–78)
	12–23.99	3	0.93 (0.59–1.46)	0.63	40 (0–66)
	24–35.99	3	0.69 (0.20–2.42)	0.036	70 (0–91)
Age at time of event ≥ 65 years					
	Lifetime abstainer	4	1.00		
	2.5–11.99	4	0.87 (0.72–1.05)	0.11	51 (0–84)
	12–23.99	4	1.00 (0.68–1.47)	0.17	0 (0–80)
	24–35.99	2	0.95 (0.68–1.32)	0.29	10 (0–41)

Abbreviations: CI, confidence interval.