Addiction

REVIEW

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

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## 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 versus 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 one to two 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.

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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, mainly for cardioprotection, as a reason for drinking alcohol [2], despite often-raised concern in the scientific literature about the causality of a cardioprotective effect.

Often 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 upwards 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 Meta-analysis Of Observational Studies in Epidemiology (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 [16–23], meta-analyses [3,24–28] 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: (i) case–control or cohort study; (ii) a measure of risk and its corresponding measure of variability was reported (or sufficient data to calculate these); (iii) IHD analysed as a separate outcome (ICD-9: 410–414, ICD-10: I20–25); (iv) 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) and (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; and (v) estimates were at least age-adjusted.

Because the focus of this meta-analysis was epidemiological 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, end-point (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 [29,30], 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 relative risk (RR) estimates and their corresponding variances, number of cases and controls or people at risk for each reported category of average alcohol intake (if not directly reported, we estimated these based on standard formulas) [31,32], 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 mid-points (mean) of reported categories. For open-ended categories we added three-quarters 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 [33]. 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 [34]. 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 life-time abstention based on a previous meta-analysis [35] to avoid the sick-quitter effect. 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 [35]. These corrections were performed 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 life-time abstainers. Those consuming >72 g/day were excluded from all analyses because of scarcity of data.

### Statistical analysis

Hazard ratios, RRs and odds ratios (ORs) were treated as measures of RR. Expecting a curvilinear relationship between alcohol and IHD risk, we used fractional polynomials [36] 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 & Longnecker [34] and Orsini *et al*. [37]. 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 [36]. Significant gain in deviance by first- and second-order models was determined by likelihood ratio tests with 1 and 2 degrees of freedom (d.f.), respectively. Goodness-of-fit statistics were used to choose the best-fitting model [38] 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 [39–41]. A significant effect modification was determined by a likelihood ratio test with 2 d.f., and subgroup 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 RR estimates. We further tested the impact of study design (cohort versus 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: (i) life-time abstainer, (ii) occasional drinker (less than weekly drinking or 0.1–2.49 g/day) and (iii) 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 one standard drink (12 g pure alcohol content) [33]. 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 [42]. We quantified between-study heterogeneity using Cochrane's $Q$ [43] and the $I^2$ statistic [44]. $I^2$ 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 [45], and sensitivity analyses for the influence of single studies on the pooled RR were conducted. All meta-analytical analyses were conducted on the natural log scale in STATA statistical software, version 10.1 [46], and $P < 0.05$ (two-sided) was considered statistically significant.

## RESULTS

Of 1538 unique citations identified in the search, 392 full papers were retrieved and scanned for inclusion (Fig. 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 9846 IHD events with 13 199 controls among case–control studies, and 6942 IHD events with end-points combined (mortality or morbidity) and 21 839 IHD events stratified by end-point among 934 639 people at risk among cohort studies were included. Overall, 38 627 IHD events in 957 684 participants contributed to this analysis. The number of cases per study ranged from 34 to 6135, and the total sample size from 309 to 245 207. The majority of selected articles originated in the United States ($n = 16$), Japan ($n = 5$) and the United Kingdom ($n = 4$), but a wide range of countries were included (Table 1). Only two studies [47,48] provided stratified estimates for race other than white. We therefore refrained from analysing those separately and included each estimate into the respective sex and end-point strata.

Among the papers selected for a quantitative analysis (Table 1), 20 papers reported only estimates for end-point or sex combined. These estimates were used in any of the respective analyses labelled as 'combined' (Tables 3 and 4, Fig. 3), whereas 24 papers reporting sex- and end-point-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 followed a *J*-curve with a nadir (lowest point of the curve, i.e. lowest IHD risk) at 31 g/day for IHD mortality (Fig. 2a). The reversion point was reached at 63 g/day. Regarding morbidity in men, a declining curve levelled off for stratified-only estimates (Fig. 2b), with the nadir at 69 g/day. Analyses using estimates that combined sex or end-point (Fig. 3a,b) showed similar curves and nadirs. In women a steep *J*-curve was observed for IHD mortality and morbidity (Fig. 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

Categorical analysis (Table 2) shows the relationship between average alcohol intake and risk of IHD for one, two and three standard drinks in comparison to life-time abstainers. Although the general form of the dose–response relationship derived from the fractional polynomial analyses was confirmed in each stratum, confidence intervals (CIs) were markedly wider, in particular for one or two drinks on average. For male mortality, a statistically significant cardioprotective association was detected for three standard drinks (RR = 0.78, 95% CI: 0.63–0.97), but not for one or two drinks of average alcohol consumption (RR = 0.89, 95% CI: 0.79–1.00 for one drink/day and RR = 0.86, 95% CI: 0.73–1.02 for two drinks/day, Table 2). Except for the category with three drinks/day, a statistically significant cardioprotective association was found for male morbidity, regardless of whether only stratified estimates were used (Table 2)

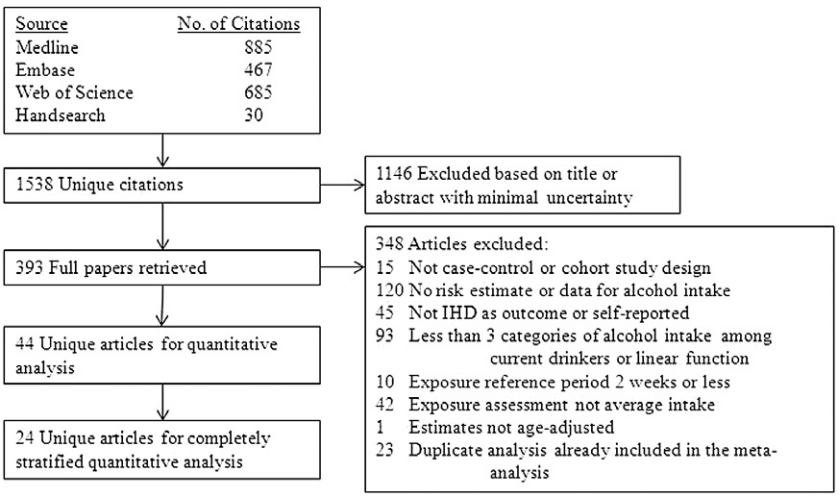


**Figure 1** Study selection process

**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.* 1980 [64] | Yes | Mortality | M | Cohort | 149 | 1832 | US | Age, diastolic BP, smoking, serum cholesterol |
| Kagan *et al.* 1981 [65] | Yes | Morbidity | M | Cohort | 113 | 7591 | US | Age |
| Gordon *et al.* 1983 [66] | Yes | Mortality | F, M | Cohort | 906 | 4625 | US | Age, systolic BP, smoking, relative weight, Sf 0–20, Sf 20–400 lipoproteins |
| Kaufman *et al.* 1985 [67] | Yes | Morbidity | M | Case–control | 1095 | 1596 | US | Age, smoking |
| Colditz *et al.* 1985 [68] | No | Mortality | Combined | Cohort | 42 | 1161 | US | Age |
| Camacho *et al.* 1987 [69] | Yes | Mortality | F, 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 |
| Scragg *et al.* 1987 [70] | Yes | Mortality, morbidity | F, M | Case–control | 594 | 2321 | New Zealand | Age |
| Kono *et al.* 1991 [71] | No | Morbidity | Combined | Case–control | 83 | 340 | Japan | Age, smoking, strenuous exercise, BMI, systemic hypertension, diabetes, parental heart disease, job class |
| Jackson *et al.* 1991 [72] | Yes | Morbidity | F, M | Case–control | 283 | 1035 | New Zealand | Age, smoking, BP, social class, exercise, recent change in drinking |
| Goldberg *et al.* 1994 [73] | 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.* 1994 [74] | Yes | Mortality | M | Cohort | 1100 | 10 604 | UK | Age, smoking, year of death, history of previous disease |
| Shaper *et al.* 1994 [75] | Yes | Mortality, morbidity | M | Cohort | 512 | 7729 | UK | Age, social class, BMI, smoking |
| Iso *et al.* 1995 [76] | No | Combined | M | Cohort | 34 | 2890 | Japan | Age |
| Rehm *et al.* 1997 [77] | Yes | Combined, mortality, morbidity | F, M | Cohort | 2112 | 6788 | US | Age, smoking |
| McElduff & Dobson, 1997 [78] | No | Combined | F, M | Case–control | 2483 | 3964 | Australia | Age, smoking, BP, high cholesterol, angina, stroke, previous MI, diabetes |
| Kitamura *et al.* 1998 [79] | No | Combined | M | Cohort | 80 | 8476 | Japan | Age, serum total cholesterol, smoking, BMI, left ventricular hypertrophy, history of diabetes |
| Maskarinec *et al.* 1998 [80] | Yes | Mortality | F, M | Cohort | 1100 | 27 678 | US | Age, race, education, BMI, smoking |
| Romelsjö & Leifman, 1999 [81] | 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 life-time, poor health, smoking |
| Hippe *et al.* 1999 [82] | No | Combined | F, M | Cohort | 1763 | 24 664 | Denmark | Age, population of origin |
| Grønbæk *et al.* 2000 [83] | No | Mortality | Combined | Cohort | 1075 | 19 006 | Denmark | Age, sex, smoking, education, physical activity, BMI |
| Liao *et al.* 2000 [84] | Yes | Mortality | F, 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.* 2001 [85] | No | Morbidity | Combined | Case–control | 155 | 309 | Bulgaria | Age, sex |
| Tavani *et al.* 2001 [86] | No | Morbidity | Combined | Case–control | 507 | 985 | Italy | Age, sex, education, physical activity, BMI, cholesterol, coffee, smoking, hyperlipidaemia, diabetes, hypertension, family history of MI |
| Sempos *et al.* 2002 [48] | No | Combined | F, M | Cohort | 244 | 1158 | US | Age |

**Table 1** *Cont.*

| *Study* | *Provided at least one stratified data set* | *End-point* | *Sex* | *Study design* | *No. of cases* | *Total sample size, No.* | *Country* | *Adjustment* |
|---|---|---|---|---|---|---|---|---|
| Romelsjö *et al.* 2003 [87] | Yes | Morbidity | F, M | Case–control | 1300 | 3534 | Sweden | Age, hospital, marital status, smoking, physical activity, cardioartherosclerotic disease, job strain, social anchorage, life control |
| Marques-Vidal *et al.* 2004 [88] | 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 |
| Wells *et al.* 2004 [89] | No | Combined | F, M | Case–control | 1164 | 2935 | New Zealand | Age |
| Fuchs *et al.* 2004 [47] | No | Combined | M | Cohort | 449 | 6276 | US | Age, smoking, BMI, LDL-level, WHR, education, income, sport index, diabetes |
| Tavani *et al.* 2004 [90] | Yes | Morbidity | F | Case–control | 558 | 1602 | Italy | Age, cohort, education, BMI, smoking, coffee, diabetes, hyperlipedaemia, BP, family history of AMI |
| Mäkelä *et al.* 2005 [91] | No | Combined | F, M | Cohort | 854 | 6392 | Finland | Age, cohort period, marital status, education, smoking |
| Kabagambe *et al.* 2005 [92] | No | Morbidity | Combined | Case–control | 1465 | 3234 | Costa Rica | Age, smoking |
| Mukamal *et al.* 2006 [93] | 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.* 2006 [94] | No | Combined | F, M | Cohort | 2032 | 53 500 | Denmark | Age, education, smoking, physical activity, BMI, total intake of vegetables, fruits, fish, and saturated fat |
| Gun *et al.* 2006 [95] | Yes | Mortality | M | Cohort | 295 | 16 547 | Australia | Age, calendar period, smoking |
| Harriss *et al.* 2007 [96] | Yes | Mortality | F, M | Cohort | 249 | 38 248 | Australia | Age, country of birth, smoking, total daily energy intake and fruit intake, saturated fat intake |
| Dorn *et al.* 2007 [97] | Yes | Morbidity | F | Case–control | 159 | 1190 | US | Age, BMI, education, race, smoking, menopausal status |
| Henderson *et al.* 2007 [98] | Yes | Mortality | M | Cohort | 572 | 70 739 | US | Age |
| Hart & Smith, 2008 [99] | Yes | Mortality, morbidity | M | Cohort | 2534 | 6000 | UK | Age |
| Ikehara *et al.* 2008 [100] | Yes | Mortality | F, M | Cohort | 736 | 83 682 | Japan | Age |
| Ikehara *et al.* 2009 [101] | Yes | Mortality | M | Cohort | 183 | 18 595 | Japan | Age |
| Bazzano *et al.* 2009 [102] | Yes | Combined, mortality | M | Cohort | 1564 | 64 597 | China | Age |
| Key *et al.* 2009 [103] | No | Mortality | Combined | Cohort | 213 | 47 254 | UK | Age, sex, smoking |
| Mukamal *et al.* 2010 [104] | No | Mortality | Combined | Cohort | 6135 | 245 207 | US | Age, sex, race, smoking, marital status, education, region, urbanization, BMI, general health status |
| Arriola *et al.* 2010 [105] | No | Combined | F, M | Cohort | 532 | 37 544 | Spain | Age, centre, smoking, height, education, physical activity, WHR, vitamin E, antithrombotic and antihaemorrhagic drugs, energy intake |

AMI: acute myocardial infarction; BMI: body mass index; BP: blood pressure; LDL: low-density cholesterol level; M: male; F: female; WHR: waist–hip-ratio; MI: myocardial infarction.

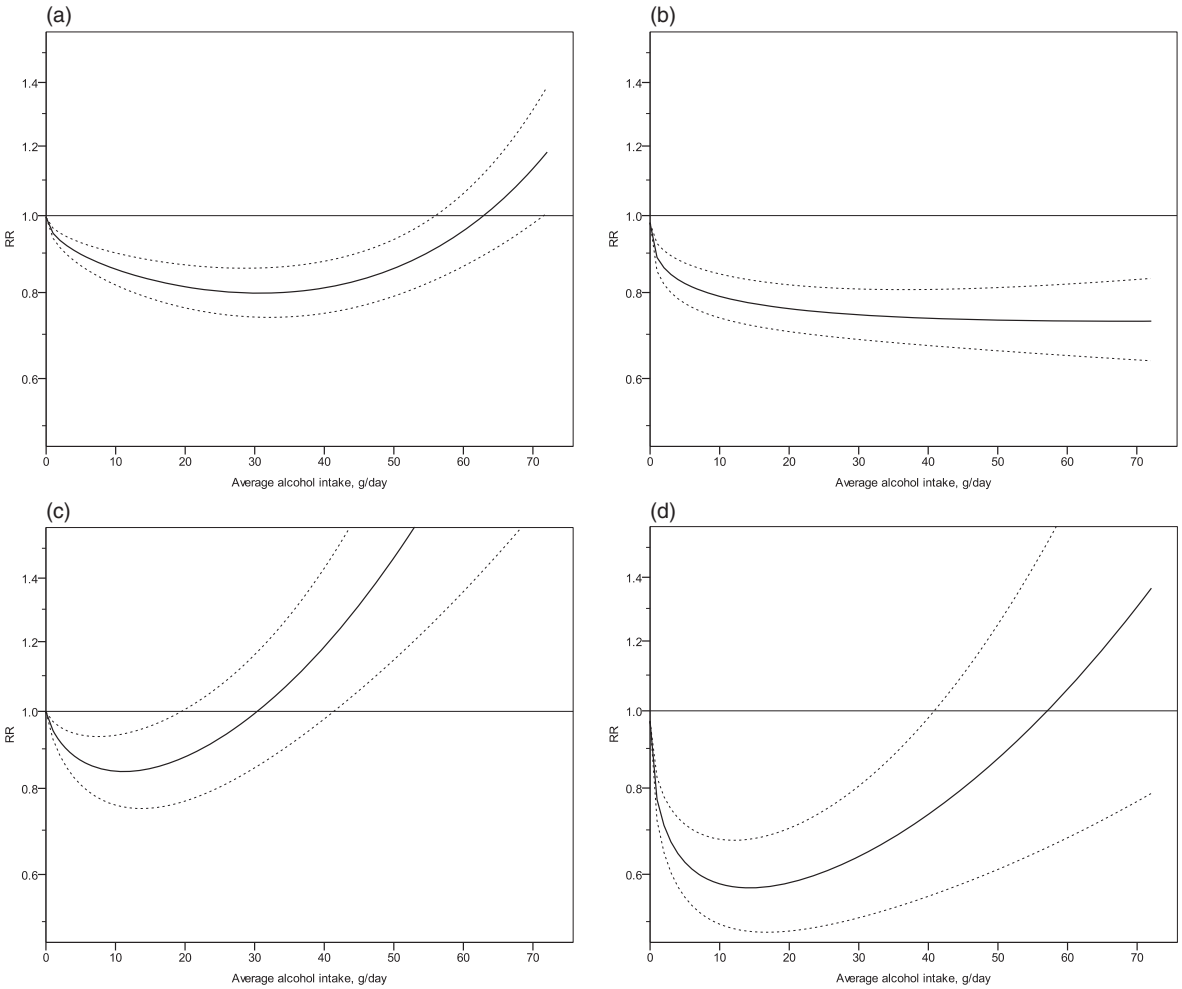


**Figure 2** Relative risk (RR) functions (solid lines, on the natural log scale) and corresponding 95% confidence intervals (dashed lines) for the dose–response relationship between average alcohol intake and risk of ischaemic heart disease (IHD), using only studies completely stratified by sex and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

or also estimates using combined sex or end-points (Table 4); however, there were only three studies available for a fully stratified analysis for three drinks of average alcohol intake. In women, using only completely stratified studies, a statistically significant association was found only for up to one standard drink on average for mortality, and for up to two drinks considering IHD morbidity. The number of studies reporting drinking levels of three 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 (Tables 2 and 4). This was expected, due in part 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 (subgroup 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 is certainly not an indicator of the strength of the evidence for a cardioprotective association, let

 

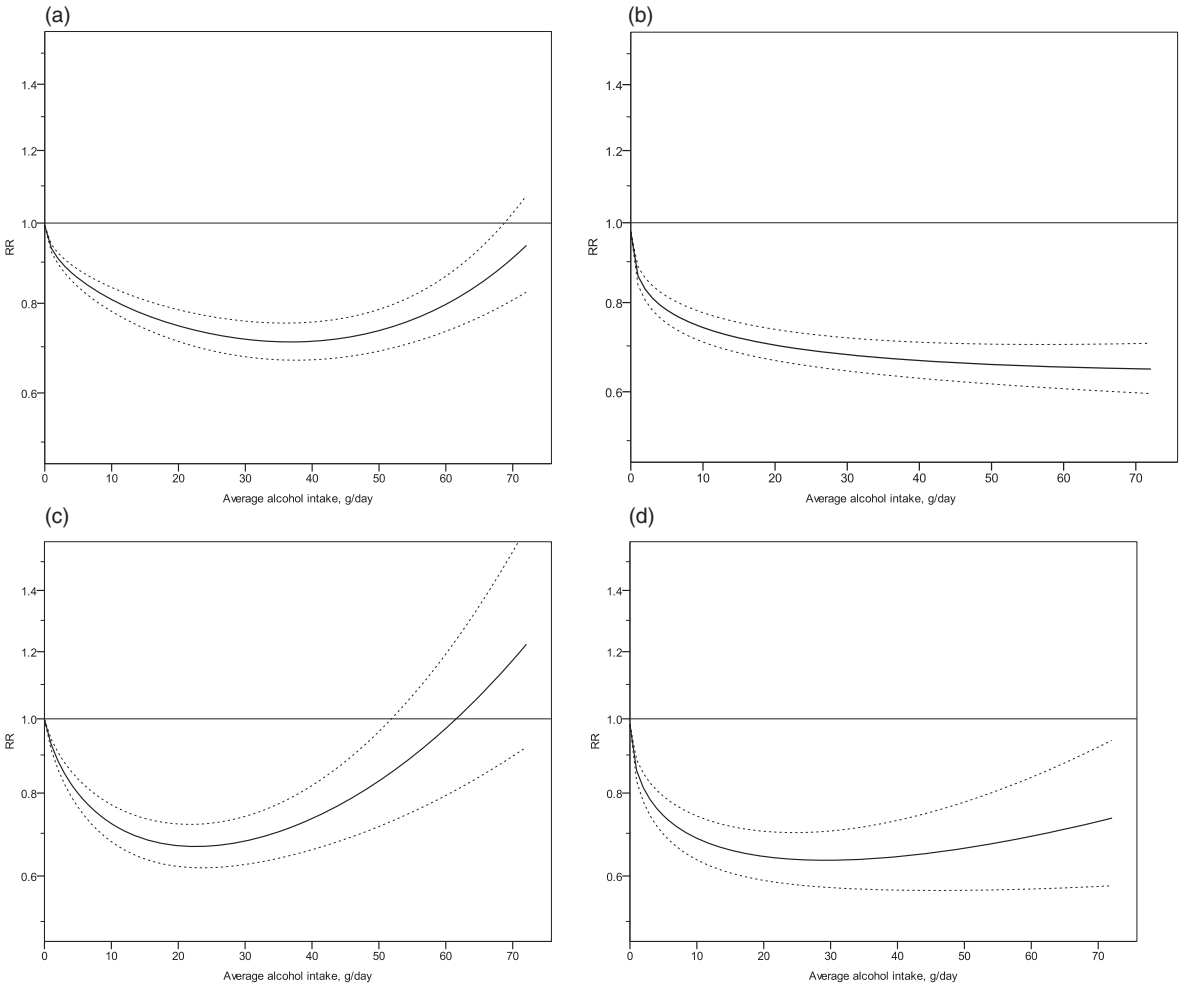


**Figure 3** Relative risk (RR) functions (solid lines, on the natural log scale) and corresponding 95% confidence intervals (dashed lines) for the dose–response relationship between average alcohol intake and risk of ischaemic heart disease (IHD), using also studies with combined sex or end-point, 1980–2010.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

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 end-point with life-time abstainers as the comparison group. The results indicate that, given current epidemiological evidence, some form of a cardioprotective association seems plausible for both sex 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 [49]. 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 (one to two 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 end-points 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

 

**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 | Life-time 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 |
| | | 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 |
| | Morbidity | Life-time 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 |
| | | 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 |
| Women | Mortality | Life-time 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 |
| | | 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 |
| | Morbidity | Life-time 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 |

Former drinkers were excluded. [a]Occasional: less than 1 drink/week or <2.5 g/day average alcohol intake; CI: confidence interval.

**Table 3** Model-based functional form and key features of the association between average alcohol intake and risk of ischaemic heart disease (IHD), by sex and end-point, 1980–2010.

| *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) |

CI: confidence interval. [a]Point where the risk function for average alcohol intake turns into a detrimental association with ischaemic heart disease.

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 (life-time abstention). CIs from the continuous analysis thus overestimate precision around the curves at low levels of consumption (one to three 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 one to three 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 life-time abstainer.

**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 | Life-time 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 |
| | | 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 |
| | Morbidity | Life-time 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) | 0.006 | 48 (15–68) | 0.99 |
| | | 24–35.99 | 16 | 1231 | 13 297 | 0.66 (0.57–0.76) | 0.004 | 55 (21–74) | 0.89 |
| Women | Mortality | Life-time 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 |
| | | 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 |
| | Morbidity | Life-time 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 |

Former drinkers were excluded. CI: confidence interval. [a]Combined end-point or sex included. [b]Occasional: less than one 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 | | | | | |
| | Life-time 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 | | | | | |
| | Life-time 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) |

CI: confidence interval.

## 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 viewpoint. 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 investigate thoroughly such interaction effects. Nevertheless, alcohol is one of the most investigated dietary risk factors for IHD [50].

Although self-reported alcohol consumption seems to be reasonably valid [8,51], some drinking and non-drinking groups change their alcohol consumption over time [52,53]. 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 end-point 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 [27]. 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 associated detrimentally with many other disease outcomes [54]. However, for low average intake, such as one to two drinks per day, we have shown that a cardioprotective association cannot be assumed readily 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 an RR of 1.45 (95% CI: 1.24–1.70) for participants with such drinking occasions versus no such drinking occasions, excluding abstainers, former drinkers where possible, occasional drinkers and regular heavy drinkers [28]. 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 that 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 [1,55].

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 [56]. 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 examine carefully 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 [57–59]. 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 answered accurately at this time [12,60,61]. Substantial heterogeneity, even at the 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 [62]. 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 one or two drinks per day as a steady daily amount of drinking have been shown to be very small, even in populations with overall low abstention rates [63].

The findings from this study support current low-risk drinking guidelines, if these recognize lower drinking limits for women. If one takes into account only average volume, this study showed that most of the cardioprotective effect can already be achieved with one to two drinks/day for men and one 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 one to two 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 [28], 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.

## Declarations of interest

J. Rehm has participated in scientific meetings organized or sponsored by the alcohol industry and received financial support for this participation. He has also received financial support for his research from governments, various national scientific research funds, the National Institutes of Health, the Canadian Institutes for Health Research and other public health-orientated agencies in Australia, Austria, Canada, Germany and the United States as well as from international organizations. All other authors have no interests to declare.

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