Chronic heavy drinking and ischaemic heart disease: a systematic review and meta-analysis

Michael Roerecke,1,2 Jürgen Rehm1,2,3,4,5

ABSTRACT
Previous meta-analyses have reported either a protective, neutral or detrimental association from chronic heavy drinking in relation to ischaemic heart disease (IHD). We investigated the potential for systematic error because of study design. Using MOOSE guidelines, studies were identified through MEDLINE, EMBASE and Web of Science up to end of March, 2014. Epidemiological studies reporting on chronic heavy drinking and IHD risk in population studies and samples of people with alcohol use disorder (AUD) were included. Random-effects meta-analysis was used to pool eligible studies. The I² statistic was used to assess heterogeneity across studies. In total, 34 observational studies with 110 570 chronic heavy drinkers and 3086 IHD events were identified. In population studies among men, the pooled risk for IHD incidence (fatal+non-fatal events) among chronic heavy drinkers (on average ≥60 g pure alcohol/day) in comparison to lifetime abstainers (n=11 studies) was relative risk (RR)=1.94 (95% CI 1.83 to 2.14), I²=54%. Few studies were available for women. In patients with AUD, the risk of IHD mortality in comparison to the general population was elevated with a RR=1.62 (95% CI 1.34 to 1.95, I²=81%) in men and RR=2.09 (95% CI 1.28 to 3.41, I²=67%) in women. There was a general lack of adjustment other than sex and age in studies among patients with AUD. There is no systematic evidence for a protective association from any type of chronic heavy drinking on IHD risk. Patients with AUD were at higher risk for IHD mortality, but better quality evidence is needed with regard to potential confounding.

INTRODUCTION
For some time the alcohol-heart relationship has been a controversial topic in heart disease epidemiology.1–3 The relationship between average alcohol consumption and ischaemic heart disease (IHD) is usually described as a J-shaped curve in epidemiological studies. Several meta-analyses have shown a protective association of some form of average alcohol consumption on IHD outcomes,2 4 5 with short-term experimental studies showing support for an effect on several surrogate biomarkers for elevated IHD risk.6 These protective associations were quite strong and comparable to preventive measures for IHD, such as physical activity.7 8 The protective association seems to be not only relatively strong in magnitude, but also to include a wide range of average alcohol consumption.2 9 In particular, one meta-analysis4 concluded that there was an inverse relation with no detrimental effect on IHD from alcohol consumption even among chronic heavy drinkers (~25% risk reduction). However, another meta-analysis5 reached a very different conclusion with regard to IHD mortality among chronic heavy drinkers (no beneficial effect), and a similar conclusion with a risk reduction for IHD morbidity (beneficial effect). This underlines the importance of stratifying analyses by IHD outcome when examining evidence for the relationship between alcohol consumption and IHD. Additionally, using current abstainers as the referent (i.e. the inclusion of former drinkers in the reference group) might lead to overestimation of any potential protective effects.10 and adjustment for potential confounding has not been optimal in many studies.11 The specific risk of chronic heavy drinking in comparison to abstainers taking into account these important conceptual and study design issues has not been systematically examined before and it is currently unclear whether chronic heavy drinking has a protective, neutral, or detrimental association with IHD. Furthermore, population studies often times miss many chronic heavy drinkers in order to maximise follow-up or because of other sampling issues.11 A good example of optimisation for follow-up availability is the Health Professionals Follow-Up Study.12 Inadvertently, these samples mostly contain more favourable drinking behaviour, such as low and regular alcohol consumption within a certain stratum of the socioeconomic continuum in high-income countries. However, as is increasingly evident in middle-income
countries, this is not the drinking pattern observed globally, which is characterised by more heavy drinking occasions.13 Among participants missed in typical cohort studies is a subgroup of chronic heavy drinkers, namely people with alcohol use disorders (AUD), who may drink considerably more than the threshold for chronic heavy drinking we use in this meta-analysis (≥60 g of pure alcohol per day).14-16 Several studies conducted among patients in treatment for AUD showed a relatively strongly elevated IHD risk.15 17 18

We hypothesised that there is no beneficial association with IHD risk in chronic heavy drinkers. Available evidence was systematically reviewed for IHD risk among chronic heavy drinkers in general population samples, and for people in AUD treatment (clinical samples). We stratified the analyses by reference group used for comparison and IHD outcomes (mortality vs morbidity). 

METHODS
Search strategy
This meta-analysis followed the MOOSE guidelines.19 Updated search strategies from three previous meta-analyses2 20 21 were used to identify observational studies reporting relative risk (RR) estimates for IHD in chronic heavy drinkers in comparison to abstainers in population samples, and to the general population in clinical samples up to 4th week of March 2014. Search terms included variations for the exposure (alcohol consumption), outcome (ischaemic heart disease) and study design (see online supplementary methods and figures S1 and S2 for details).

Inclusion criteria for the meta-analysis on chronic heavy drinking in population samples were: (1) prospective or historical cohort or case–control study design; (2) a measure of risk and its corresponding measure of variability was reported (or sufficient data to calculate these); (3) IHD was reported as a separate outcome (i.e., excluding other cardiovascular diseases, such as stroke); (4) a risk estimate for chronic heavy drinking using any type of beverage (≥60 g pure alcohol per day on average based at least on a typical week’s intake pattern) was reported among current drinkers; (5) a risk estimate for current or lifetime abstainers was reported; (6) estimates were stratified by sex and at least age-adjusted.

Inclusion criteria for the meta-analysis on AUD in clinical samples were: (7) prospective or historical cohort study; (8) a mortality risk estimate for patients with AUD was reported in comparison to the general population; (9) IHD was reported as a specific outcome; (10) a measure of risk and its corresponding measure of variability was reported (or sufficient data to calculate these); (11) estimates were stratified by sex and at least age-adjusted.

Data extraction
From all relevant articles we extracted authors’ names, year of publication, country, calendar year(s) of baseline examination, follow-up period, setting, assessment of IHD, assessment of alcohol consumption or AUD diagnosis, mean and range of age at baseline, sex, number of observed IHD cases among participants by drinking group, number of total participants by drinking group, adjustment for potential confounders and RR and its SE. The most adjusted RR reported was used, and priority was given to estimates comparing chronic heavy drinking to lifetime abstainers.

Definition of chronic heavy drinking and reference groups
Heavy drinking is not uniformly defined.22 In this meta-analysis, chronic heavy drinking was defined as all drinking groups where the lower limit was at least 60 g/day. Clinical samples (patients with AUD) are generally missed in population studies, but they can be seen as similar in terms of heavy alcohol intake although a clear definition of alcohol intake in g/day is not possible.14 The clinical sample of patients with AUD was defined by a diagnosis of AUD by entering an alcohol treatment programme in a specialised treatment facility (this includes Diagnostic and Statistical Manual (DSM-III and IV) ‘alcohol abuse and dependence’ and International Classification of Diseases (ICD-9 and 10) ‘alcohol use disorders’). Lifetime abstainers are defined as non-drinking groups where former drinkers were excluded. Current abstainers include both lifetime abstainers and former drinkers.

Outcome ascertainment
Self-reported IHD outcomes were excluded. In population samples, IHD was defined based on standard criteria ascertained by death records (death certificate, and in some cases autopsy findings), standard criteria for myocardial infarction by WHO criteria,23 24 ICD-7: 420–422, ICD-8: 410–414, ICD-9: 410–414, ICD-10: I20–I25, or by committee decision based on medical records. In clinical samples, several versions of ICD were used in primary studies, but all studies were based on death certificates, sometimes using additional sources of information about the cause of death. For this meta-analysis we have categorised IHD outcomes into three groups: (1) IHD incidence (fatal or non-fatal events), (2) IHD mortality (fatal events only) and (3) IHD morbidity (non-fatal events only).

Quality assessment
Most quality scores are tailored for meta-analyses of randomised trials of interventions25–28, and many criteria do not apply to epidemiological studies like the ones examined here. Also, their use in meta-analyses remains controversial.28 29 Thus, quality assessment was incorporated differently by including quality components such as study design and alcohol measurement into the inclusion and exclusion criteria (see online supplementary table S1 and methods for details). One author performed the literature search and abstracted the data. To control for subjectivity, 10 papers were randomly
selected and extracted by another author. No changes in abstraction were recorded. Information found in related papers from the same cohort was used where possible. Authors from primary studies were not contacted in case insufficient information was provided.

Statistical analysis
Standardised mortality ratios, HRs, ORs and RRs were treated as equivalent measures of risk. We calculated the overall pooled risk of IHD events associated with chronic heavy drinking stratified by sex and reference group, and conducted subanalyses stratified by assessment of IHD outcome (fatal and non-fatal events). IHD incidence included combined fatal and non-fatal events, or each respective outcome if only this was reported. When more than one estimate from primary studies was assigned to an IHD category, we combined the reported results using fixed-effects to derive one effect estimate per study separately for each analysis or subanalysis; chronic heavy drinking groups were combined using the method by Hamling et al. RRs were pooled across studies using inverse-variance weighted DerSimonian-Laird random-effect models to allow for between-study heterogeneity. Between-study heterogeneity was quantified using the $I^2$ statistic. $I^2$ can be interpreted as the proportion of the total variation in the estimated effects for each study that is due to heterogeneity between studies. We conducted meta-regression analyses to identify study characteristics that influenced the association between chronic heavy drinking and IHD. Potential publication bias was examined using Egger’s regression-based test. All regression-based tests were only conducted when 10 or more data points were available. Sensitivity analyses for the influence of single studies on the pooled RRs were conducted omitting studies one by one and re-estimating the pooled RR. All meta-analytical procedures were conducted on the natural log scale in Stata statistical software, V.11.2 (Stata Corp, College Station, Texas, USA).

RESULTS

Literature search
In total 34 unique articles meeting the inclusion criteria were used in this meta-analysis (see online supplementary table S1). Overall, 8 studies were conducted in the USA, 5 in Sweden and 4 in Japan, but articles from 20 countries were included altogether. Two papers provided pooled individual data from several studies. The analysis was based on 3086 observed IHD events (fatal and non-fatal) among 110 570 chronic heavy drinkers. Average weighted follow-up time was 11.7 years in population samples and 10.4 in clinical samples. Regarding population samples, most excluded IHD disease at baseline or adjusted for prevalent IHD and smoking at baseline. Ten studies provided data from patients with AUD treatment (clinical samples), mostly standardised (by age and sex) mortality ratios (see online supplementary table S1 for details).

Meta-analyses
IHD risk among chronic heavy drinkers in men is displayed in table 1. Among population samples, 11 studies provided data with lifetime abstainers as the reference group and 14 with current abstainers. The pooled risk for IHD incidence among chronic heavy drinkers in comparison to lifetime abstainers was RR=1.04, 95% CI 0.83 to 1.31, n=11 studies, figure 1), IHD mortality risk was similar (RR=1.00, 95% CI 0.74 to 1.36). Heterogeneity was moderate (for IHD incidence $I^2=54\%$). In comparison to a reference group which contains current abstainers, pooled risks among chronic heavy drinkers were consistently lower (RR point estimates between 0.78 and 0.85, IHD incidence was statistically significant with RR=0.83, 95% CI 0.70 to 0.98, figure 2) compared to examinations using lifetime abstainers as the reference group. Heterogeneity was more pronounced in studies using current abstainers as the reference group (for IHD incidence $I^2=73\%$). Five studies reported IHD morbidity risk among chronic

| Heavy drinking group, IHD end point | Reference group | Number of studies | Number of events* | Number of chronic heavy drinkers | Relative risk | 95% CI | p Value† | $I^2$ (%) |
|-----------------------------------|----------------|-----------------|------------------|-------------------------------|---------------|-------|---------|----------|
| Chronic heavy drinking (population samples) | | | | | | | | |
| Incidence | Lifetime abstainers | 11 | 954 | 35 756 | 1.04 | 0.83 to 1.31 | 0.016 | 54 |
| Mortality | Lifetime abstainers | 5 | 618 | 34 182 | 1.00 | 0.74 to 1.36 | 0.026 | 64 |
| Morbidity | Lifetime abstainers | 3 | 299 | 471 | 1.13 | 0.78 to 1.63 | 0.97 | 0 |
| Incidence | Current abstainers | 14 | 1268 | 50 805 | 0.83 | 0.70 to 0.98 | <0.001 | 73 |
| Mortality | Current abstainers | 9 | 853 | 46 450 | 0.85 | 0.67 to 1.08 | <0.001 | 74 |
| Morbidity | Current abstainers | 2 | 193 | 884 | 0.78 | 0.21 to 2.90 | 0.006 | 87 |
| Patients with AUD (clinical samples) | | | | | | | | |
| Mortality | General population | 9 | 761 | 18 758 | 1.62 | 1.34 to 1.95 | <0.001 | 81 |

See Methods section for definitions of chronic heavy drinking groups.

*In chronic heavy drinking groups.
†For heterogeneity (Cochran’s Q).
heavy drinkers, three with lifetime abstainers (RR=1.13, 95% CI 0.78 to 1.63) and two with current abstainers as the reference group (RR=0.78, 95% CI 0.21 to 2.90). There were not enough studies to further investigate IHD morbidity. Among patients with AUD the risk of IHD mortality in comparison to the general population was substantially elevated with RR=1.62 (95% CI 1.34 to 1.95) among men (figure 3).

There were only 114 IHD events reported in women, of which 75 were among patients with AUD. The pooled RR for IHD mortality among patients with AUD (n=5 studies) was 2.09 (95% CI 1.28 to 3.41, figure 4).

**Publication bias and sensitivity analyses**
Tests for publication bias or meta-regressions were not conducted in most analyses because of the small number of studies available for each analysis. Two analyses with enough studies (IHD incidence risk in chronic heavy drinkers compared to lifetime and current abstainers in men) did not reveal evidence for such bias (p=0.46, and 0.35, respectively, see online supplementary figures S3 and S4 for funnel plots). Omitting studies one by one and re-estimating the pooled risks did not change conclusions in any of the analyses. Using meta-regression, study design (case–control vs cohort studies) did not reveal a significant association for analyses on IHD incidence in chronic heavy drinkers compared to lifetime abstainers (p=0.22).

The pooled risk for IHD incidence among chronic heavy drinkers in population samples with lifetime abstainers as the reference group that adjusted for age and smoking status (n=8 studies) was virtually unchanged with RR=1.04 (95% CI 0.82 to 1.33). The risk for IHD incidence among chronic heavy drinkers in population samples, which, in addition to age and smoking status, also adjusted for either physical activity, body mass index or at least one socioeconomic indicator was RR=0.97 (95% CI 0.79 to 1.18, n=6 studies). A similar sensitivity analysis with current abstainers as the reference group revealed a pooled RR=0.75 (95% CI 0.62 to 0.91) and RR=0.72 (95% CI 0.58 to 0.89). In contrast, only one study among patients with AUD adjusted for risk factors other than age, race, calendar year or follow-up length. Therefore, such analyses were not conducted among clinical samples.

**DISCUSSION**
Our analysis showed that when the comparison group was lifetime abstainers in population studies, there was no indication for a protective association from chronic heavy drinking, contrary to our analysis using current abstainers as the reference and results from another meta-analysis, which reported a universal protective association between alcohol consumption and IHD. However, when current abstainers were the reference...
The difference regarding the reference group was also evident within primary studies, where the risk was below RR=1 when current abstainers were the reference group, and above 1 when lifetime abstainers were the reference group. As most of the studies reported on mortality and only few studies examined IHD morbidity in comparison to lifetime abstainers, we were unable to draw firm conclusions about the relationship between chronic heavy alcohol consumption and IHD morbidity. More systematic research is needed in this area.

With regard to population studies, adjustment for confounders was not optimal in many studies; however subgroup analyses of studies with good adjustment did not change our conclusions (no beneficial association between chronic heavy alcohol consumption and IHD risk). In contrast to chronic heavy drinkers from population samples, clinical samples of patients with AUD showed a clear detrimental association with a 62% higher risk of heart disease mortality compared to the general population among men, and a twofold higher risk among women. However, there was an apparent lack of adjustment other than age and sex, and lack of recent studies investigating IHD among patients with AUD with only two studies with a baseline assessment after 1990. In particular, the complete lack of adjustment for smoking in clinical samples shows that better quality evidence is needed to confirm the role of alcohol consumption on IHD risk in patients with AUD. As the control group was the general population for clinical samples, the risk for mortality and few studies examined IHD morbidity in comparison to lifetime abstainers,
Figure 3  Forest plot of the association between ischaemic heart disease mortality and alcohol use disorder in clinical samples in comparison to the general population in men, 1967–2012.

Figure 4  Forest plot of the association between ischaemic heart disease mortality and alcohol use disorder in clinical samples in comparison to the general population in women, 1967–2012.
IHD should be expected to be somewhat higher compared to population sample results (when the reference was lifetime abstainers) if one assumes a protective effect of moderate alcohol consumption. A recent meta-analysis on average alcohol consumption has shown strong evidence from observational studies that the risk of IHD among moderate drinkers is reduced in comparison to lifetime abstainers. Among those reporting the strongest elevated risk for IHD are studies from Russia. However, because there are very few abstainers, the reference group is typically not abstainers, but people with low average alcohol intake. A relatively frequent consumption pattern in Russia is episodic heavy to very heavy consumption with sometimes prolonged binges (‘zapoi’, an episode of continuous drunkenness lasting two or more days in combination with withdrawal from normal social life). This drinking pattern is so extreme that it is heavy with regard to both average and episodic consumption. Nevertheless, the risk among heavy alcohol drinkers in comparison to low level drinkers was substantial, which points to no beneficial effects from heavy alcohol intake and is in support of our findings.

Limitations
The analysis was limited to English-language, German-language and Spanish-language studies, leaving the possibility of unidentified studies. Furthermore, as is the case for all meta-analyses, our analysis was subject to bias and uncontrolled confounding as they were inherent in the primary studies. I² values were moderate to high in most analyses. Although adjustment for major IHD risk factors was investigated in population studies and did not result in a change of conclusions, adjustment for risk factors other than age and smoking was not optimal in most studies, and uncontrolled confounding may have contributed to any observed between-study heterogeneity. Uncontrolled confounding might have been most problematic in the clinical samples used in our study, which did not control for smoking or any other IHD risk factor other than sex and age. The choice of random-effect models (although giving more weight to smaller studies) was justified by the amount of heterogeneity detected and because epidemiological studies generally cannot control unobserved confounding in the same way a randomisation process can. However, conclusions were not affected by this choice. Nevertheless, all studies were observational and thus causality cannot be established. Ill-definition of cardiovascular deaths and substantial variation across countries in terms of the quality of classifications of IHD deaths may pose an additional problem. In a Swedish sample included in our analysis, Denison examined information from death certificates and independent evaluations from hospital and clinical autopsy reports, police reports, forensic autopsy reports and toxicology reports. They found only a slightly higher mortality risk for cardiovascular diseases compared to death certificate information. As we focused on high-quality epidemiological studies, we excluded self-reported IHD morbidity and other forms of heart disease not defined by ICD-10: I20–I25, and thus cannot generalise beyond the populations and outcomes in our study.

Study quality was substantially lower in clinical samples because of lack of adjustment for potential confounding. Only one study reported risk estimates adjusted for more than just age, one other study also adjusted for length of follow-up. Thus, confounding or effect modification from factors other than age and sex could not be examined. It seems likely that, given the close correlation of smoking with alcohol consumption in general and at high levels of alcohol consumption in particular, smoking had some undetected influence on IHD mortality in clinical samples because of a clearly established monotonous detrimental relationship of smoking with heart disease. However, there is surprisingly little research on this topic and it remains to be seen whether smoking explains the elevated risk for IHD seen in patients with AUD. Few studies have examined IHD risk stratified by alcohol and smoking in population studies, but no clear picture emerged. In particular, there are no studies investigating potential joint effects from smoking and chronic heavy alcohol consumption on IHD risk with lifetime abstainers as the reference group. If alcohol consumption in patients with AUD is the determining factor for an increased risk of IHD, evidence from AUD treatment outcome studies could provide further pieces of evidence for a potential causal effect. Many studies among patients with AUD showed that a reduction from chronic heavy drinking to moderate or low levels, including but not limited to abstinence, can substantially reduce all-cause mortality. However, there seems to be no investigations regarding whether or not IHD as a cause of death played a substantial role in this reduction of all-cause mortality.

Experimental evidence for chronic heavy drinking and heart disease risk
What is the underlying experimental evidence base? Long-term randomised studies on IHD mortality or morbidity are unavailable. Although regular low to moderate alcohol intake has been found to have beneficial, dose-dependent effects on biomarkers for IHD in short-term experimental studies, mainly by increasing high-density lipoprotein (HDL) levels, inhibiting platelet activation, reducing fibrinogen levels and producing anti-inflammatory effects, chronic heavy drinking has been found to be related to detrimental effects on the heart, with adverse effects mainly on blood pressure, fibrinolytic factors and ventricular arrhythmia after cessation of heavy drinking, as well as in participants with existing ischaemic disease through silent myocardial ischaemia and angina. Chronic alcohol intake in particular is associated with physiological changes of the heart, including prolonged QT intervals and electrolyte abnormalities. There are some short-term experimental
studies specifically on regular heavy drinking. During heavy alcohol intake, trygliceride levels were elevated in most studies,\textsuperscript{17–50} with transient positive effects on trygliceride in one study,\textsuperscript{51} and HDL cholesterol was elevated in all studies.\textsuperscript{47–52} In fact, the highest HDL levels are observed in people with AUD.\textsuperscript{53} It seems that despite a beneficial effect on HDL cholesterol even in chronic heavy alcohol consumers, other effects of chronic heavy alcohol consumption on heart disease risk might negate those beneficial effects,\textsuperscript{54–55} resulting in an overall neutral or detrimental association found in our analysis.

Further work on distinct biochemical pathways and differentiation of heart disease outcomes should be a priority in alcohol-heart research.

Conclusions

As the evidence base is scarce in women, we restrict our findings to men only. Our findings, in combination with previous investigations,\textsuperscript{2–20} lead to three main conclusions: First, there is no systematic evidence of a protective association between IHD and chronic heavy drinking. Second, the findings show that the reference category is crucial in determining IHD risk from any type of alcohol consumption. Public perception of a universal cardioprotective association, however, might overshadow these important parts of the alcohol-heart relationship, as it can be used as an excuse for heavier drinking. Third, a detrimental association of alcohol consumption on IHD is evident only for patients with AUD, the highest end of the spectrum of alcohol consumption. It should be stressed that there is a clear detrimental effect of any heavy drinking episodes on injuries and through overall intake on many cancers.\textsuperscript{56–57} Thus heavy drinking in all forms should be discouraged.

Contributors

All authors have contributed to the writing of this review article and are responsible for the overall content.

Competing interests

None.

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Chronic Heavy Drinking and Ischaemic Heart Disease: A Systematic Review and Meta-Analysis

SUPPLEMENTARY MATERIAL

Supplementary Methods

Systematic Review Protocol

Supplementary Figures

Supplementary Figure 1. Search Results for Population Studies on Chronic Heavy Alcohol Consumption and Ischaemic Heart Disease Risk

Supplementary Figure 2. Search Results for Patients With Alcohol Use Disorder (AUD, Clinical Samples) and Ischaemic Heart Diseases Mortality

Supplementary Figure 3. Funnel Plot for Ischaemic Heart Disease incidence Among Chronic Heavy Drinkers with Lifetime Abstainers as The Reference Group

Supplementary Figure 4. Funnel Plot for Ischaemic Heart Disease incidence Among Chronic Heavy Drinkers with Current Abstainers as The Reference Group

Supplementary Tables

Supplementary Table 1. Characteristics of 34 Studies for Ischaemic Heart Disease in Heavy Drinkers, 1967-2012
Supplementary Methods

Systematic Review Protocol

Title: Systematic review and meta-analysis of heavy drinking and ischaemic heart disease

Protocol Information

Dates
All searches were conducted in week 4 of March 2014.

Stage
Review completed in April 2014.
Current stage: Meta-analysis completed.

Collaborators
None.

Review Methods

Review questions
What is the relative risk for ischaemic heart disease among heavy drinkers?

Context
Specific risk of chronic heavy drinking for ischaemic heart disease (IHD) in comparison to lifetime abstainers has not been systematically examined before and it is currently unclear whether chronic heavy drinking has a protective, neutral, or detrimental association with IHD. Population studies often miss many chronic heavy drinkers in order to maximize follow-up or because of other sampling issues [1]. Inadvertently, these samples mostly contain more favorable drinking behavior, such as low and regular alcohol consumption within a certain stratum of the socioeconomic continuum in high income countries. However, as is increasingly evident in middle income countries, this is not the drinking pattern observed globally [2]. Among participants missed in typical cohort studies is a subgroup of chronic heavy drinkers, namely people with alcohol use disorders (AUD), who drink on average considerably more than our threshold for heavy drinking [3 4].

Condition or domain
Ischaemic heart disease (morbidity or mortality).

Primary outcomes
Incidence of IHD events.

Secondary outcomes
Fatal and non-fatal IHD events.

Intervention/exposure
Chronic heavy drinking is the exposure of interest.

**Comparators/controls**
Standardized mortality rates compared to the general population or measure of relative risk in comparison to abstainers (current or lifetime).

**Types of studies to be included initially**
Observational studies (historical or prospective cohort and case-control studies).

**Literature searches**
Using PRISMA and MOOSE guidelines [5 6], we conducted two systematic searches using electronic databases from their inception (clinical samples) or 1980 (population samples) to fourth week of March 2014 for original articles, excluding letters, editorials, conference abstracts, reviews, and comments for variations of search terms for the exposure (alcohol consumption), outcome (IHD), and study design. Additionally, we hand searched references of identified papers and relevant reviews and meta-analyses.

**Participants/population**
Inclusion criteria: Adults (≥15 years) from population samples or clinical samples (patients with AUD in treatment), IHD was analyzed as a separate outcome (ICD-9: 410-414, ICD-10: I20-25), a measure of risk and its corresponding measure of variability was reported (or sufficient data to calculate these), and English-, German-, or Spanish-language.
Exclusion criteria: Adolescents (<15 years), population samples from people with IHD-related conditions. We excluded self-reported IHD outcomes, as well as studies reporting estimates on cardiovascular outcomes combined rather than IHD separately and studies with precursors as outcome.
Further inclusion criteria for population studies:
Case-control or prospective or historical cohort study design, exposure measurement had to cover a reference period of more than 2 weeks for average alcohol consumption at baseline.
Further inclusion criteria for clinical studies:
Prospective or historical cohort study design, mortality risk for diagnosed participants currently in AUD treatment (in- or out-patient, this includes DSM-III and IV ‘alcohol abuse and dependence’ and International Classification of Diseases [ICD-9 and 10] ‘harmful use’ or ‘non-dependent alcohol abuse’ and ‘alcohol dependence’) compared with the general population.

**Searches**

**Population samples**
Databases searched: MEDLINE, EMBASE, Web of Science (Science Citation Index Expanded, Social Sciences Citation Index, Arts & Humanities Citation Index), and ETOH (Alcohol and Alcohol Problems Science Database, National Institute on Alcohol Abuse and Alcoholism, January 1980–December 2003).
Search strategy in Medline (through OVID):
Clinical samples
Databases searched: MEDLINE, EMBASE, Web of Science (Science Citation Index Expanded, Social Sciences Citation Index, Arts & Humanities Citation Index), and ETOH (Alcohol and Alcohol Problems Science Database, National Institute on Alcohol Abuse and Alcoholism, January 1980–December 2003).

Search strategy in Medline (through OVID):

URL to search strategy
None.

Data extraction
From all relevant articles we extracted authors’ names, year of publication, country, calendar year(s) of baseline examination, follow-up period, setting, assessment of IHD and alcohol consumption or AUD diagnosis, mean and range of age at baseline, sex, number of observed IHD cases or deaths among participants by drinking group, number of total participants by drinking group, adjustment for potential confounders, and RR and its standard error. We used the most adjusted RR reported, and gave priority to estimates comparing heavy drinking to lifetime abstainers were abstracted by one reviewer. Full-text articles with uncertain eligibility were discussed by both authors until consensus was reached. To control for subjectivity, 10 papers were randomly selected and extracted by another author. No changes in abstraction were recorded. Primary
authors were not contacted by the authors in case there was not enough information presented in the article.

Risk of bias
Most quality scores are tailored for meta-analyses of randomized trials of interventions [7-10] and many criteria do not apply to epidemiological studies like the ones examined here. Also, their use in meta-analyses remains controversial [10 11]. Thus, quality assessment was incorporated differently by including quality components such as study design and alcohol measurement into the inclusion and exclusion criteria (please see also Data abstraction and Supplementary Table 1 for details). Quality checklists therefore would not have been able to distinguish the quality of selected studies in our analysis.

Strategy for data synthesis
Standardized mortality ratios (i.e. comparisons of mortality risks of patients in AUD treatment with the sex- and age-specific general population; see [12]), hazard ratios, odds ratios, and relative risks were treated as equivalent measures of risk. Analyses were stratified by sex where possible. If necessary, relative risks within studies were re-calculated based on the method described by Hamling et al. [13] and pooled across studies using inverse-variance weighted DerSimonian-Laird random-effect models to allow for between-study heterogeneity [14]. We quantified between-study heterogeneity using Cochran’s Q [15] and the I² statistic [16]. I² can be interpreted as the proportion of the total variation other than chance that is due to heterogeneity between studies. We tested for potential publication bias using Egger’s test [17]. Sensitivity analyses for the influence of single studies on the pooled relative risks were conducted omitting one study at a time and re-estimating the pooled relative risk. No change in conclusions was observed. All meta-analytical procedures were conducted on the natural log scale in Stata statistical software, version 12.1 (Stata Corp, College Station, Texas), and p<0·05 (two-sided) was considered statistically significant.

Analysis of subgroups or subsets
Subgroup analyses were completed for different classification of alcohol exposure (chronic heavy drinking based on average alcohol consumption and AUD patients in treatment), and for incidence, mortality,morbidity, and adjustment for confounders. Meta-regression was conducted to identify study characteristics (study design) that might influence the association between heavy drinking and IHD in all subgroups considered when more than 10 studies were available.

Type of review
Prognostic.

Language
English, Spanish, German.

Country
Canada.
Dissemination plans
Publication in peer-review journal.

Keywords
Heavy drinking, alcohol use disorder, heart disease, incidence, mortality, systematic review, meta-analysis

Details of any existing review of the same topic by the same authors
None.

Review status
Completed, but not published.
Supplementary Figure 1. Search Results for Population Studies on Chronic Heavy Alcohol Consumption and Ischaemic Heart Disease Risk

Articles identified:
- MEDLINE (n=1294)
- EMBASE (n=661)
- Web of Science (n=1258)
- Handsearch (n=2)

Unique articles (n=2769)

Excluded based on title or abstract with minimal uncertainty (n=2306)

Articles retrieved in full-text (n=463)

Articles excluded (n=449):
- Not case-control or cohort study design (n=21)
- No data for alcohol intake (n=198)
- IHD is not the outcome or self-reported (n=64)
- No data on chronic heavy drinking (n=135)
- Estimates not age-adjusted (n=1)
- Reference group is not lifetime abstainers (n=19)
- No deaths recorded (n=1)

Articles for quantitative analysis:
- Chronic heavy drinking (n=24)
- Lifetime abstainers are reference (n=11)
- Current abstainers are reference (n=13)
**Supplementary Figure 2.** Search Results for Patients with Alcohol Use Disorder (AUD, Clinical Samples) and Ischaemic Heart Diseases Mortality

Articles identified in search:
- MEDLINE (n=385)
- EMBASE (n=225)
- Web of Science (n=1123)
- Handsearch (n=6)

Unique articles (n=1608) excluded based on title or abstract with minimal uncertainty (n=1392)

Articles retrieved in full-text (n=216) excluded:
- Exposure not AUD (n=32)
- Not cohort study design (n=16)
- No control group (n=36)
- Not age-adjusted (n=5)
- Duplicate reports on the same study population (n=15)
- No cause-specific mortality (n=88)
- Not currently in AUD treatment (n=5)
- General population is not control group (n=2)
- IHD not reported (n=7)

Articles for quantitative analysis (n=10)
**Supplementary Figure 3.** Funnel Plot for Ischaemic Heart Disease Incidence among Chronic Heavy Drinkers with Lifetime Abstainers as the Reference Group

Effect size is log(RR)
Supplementary Figure 4. Funnel Plot for Ischaemic Heart Disease Incidence among Chronic Heavy Drinkers with Current Abstainers as the Reference Group

Effect size is log(RR)
**Supplementary Table 1.** Characteristics of 34 Studies for Ischaemic Heart Disease Risk in Chronic Heavy Drinkers, 1967-2012

| Source | Sex, Age at baseline | Location, baseline period | Setting | No. of heavy drinkers (IHD events/ total participants) | IHD assessment | Heavy drinking definition | Reference category | Adjustment |
|--------|---------------------|---------------------------|---------|-------------------------------------------------------|----------------|--------------------------|-------------------|------------|
| **Population samples** | | | | | | | | |
| Dyer et al., 1981[18] | M, 40-55 | US, 1957-74 | Chicago Western Electric Company Study | 12/78 | Mortality, ischaemic heart disease (not defined) | ≥77 g/day average (based on total intake per month) | Lifetime abstainers | Age (participants free of definite ischaemic heart disease) |
| Kaufman et al., 1985[19] | M, 30-55 | US, 1980-83 | Hospital-based, North eastern US (78 hospitals) | 209/299 | Morbidity, first MI (WHO criteria) | ≥67 g/day average (based on typical frequency and amount) | Lifetime abstainers | Age (no history of MI or angina pectoris among controls) |
| Jackson et al., 1991[20] | M, 25-64 | New Zealand, 1986 | Auckland | 33/68 | Incidence (fatal and non-fatal events mortality and morbidity were reported separately), MONICA criteria | >81 g/day (based on typical frequency and amount last 3 months) | Lifetime abstainers | Age, smoking, hypertension, social class, exercise, recent (12 months) change in drinking |
| Iso et al., 1995[21] | M, 40-69 | Japan, 1975-87 | Ikawa, Honjo and Kyowa | 4/439 | Incidence (fatal + non-fatal events), WHO criteria for ischaemic heart disease (definite or suspected MI, angina pectoris, sudden death) MONICA criteria | ≥70 g/day average (based on usual weekly intake) | Lifetime abstainers | Age, hypertension, serum total cholesterol, smoking, diabetes (history of ischaemic heart disease or stroke were excluded) |
| McElduff & Dobson 1997[22] | M, 35-69 | Australia, 1983 | New South Wales (MONICA) | 89/103 | Incidence (fatal + non-fatal events), definite MI, possible MI, or coronary | ≥90 g/day typical amount per drinking day on 5-6 days per week or daily | Lifetime abstainers | Age, smoking, BP, cholesterol, angina, stroke, MI, diabetes |
| Study                        | Gender | Age Range | Country | Study Design | Incidence | Mortality | Mortality Criteria | Lifetime Abstainers | Age Factor(s)                                                                 |
|------------------------------|--------|-----------|---------|--------------|------------|------------|-------------------|---------------------|-----------------------------------------------------------------------------|
| Rehm et al., 1997[23]        | M, W   | 18+       | US      | NHANES I     | 15/61      | ≥72 g/day | Incidence (fatal + non-fatal events) | Lifetime abstainers | Age                                                                        |
| Kitamura et al., 1998[24]    | M      | 40-59     | Japan   | Osaka        | 6/580      | ≥69 g/day | Incidence (fatal + non-fatal events) | Lifetime abstainers | Age, serum total cholesterol, smoking, BMI, left ventricular hypertrophy, history of diabetes |
| Klatsky et al., 2003[25]     | M, W   | 18+       | US      | Kaiser Permanente, California | 88 a /2004 | ≥6 drinks daily | Mortality, ICD-9: 410-414 from death certificates | Lifetime abstainers | Age, race, BMI, education, marital status, smoking, IHD symptoms at baseline |
| Romelsjö et al., 2003[26]    | M      | 45-70     | Sweden  | Stockholm Heart Epidemiology Program (SHEEP) | 81/153    | ≥70 g/day average | Incidence (fatal + non-fatal events), morbidity was reported separately, (all first MI, based on death certificate, autopsy findings, or medical records) | Lifetime abstainers | Age, hospital, marital status, SES, smoking, physical activity, cardioatheriosclerotic disease, job strain, social anchorage, life control |
| Inoue et al., 2012[27]       | M      | 35-101    | Japan   | Pooled analysis of 6 large cohort studies in Japan | 228/12 393 | ≥69 g/day average | Mortality based on death certificates, ICD-10: I20-25 | Lifetime abstainers | Age, area, smoking, BMI, hypertension, diabetes, leisure time physical activity |
| Bergmann et al., 2013[28]    | M      | 25-70     | Europe (23 centres in 10 | EPIC | 302/20 228 | >60 g/day (based on amount per week) | Mortality (record linkage with death) | Lifetime abstainers | Stratified by age and centre; adjusted for BMI, height, |
| Study                          | Gender | Age | Country/Region | Health examination/registry | Cases/Total | ICT-10/9 | Risk | Current abstainer | Additional variables |
|-------------------------------|--------|-----|----------------|------------------------------|-------------|----------|------|-------------------|---------------------|
| Friedman & Kimball 1986[29]   | M, 30-59 | US, 1948-72 | Framingham Heart Study, Massachusetts | 15/138 | I20-25 | ≥67 g/day average (based on total intake per month) | Current abstainer | Age (all participants free of ischaemic heart disease at baseline) |
| Shaper et al., 1987[30]       | M, 40-59 | UK, 1978-85 | British Regional Heart study | 22/631 | ICD-9: 410-414, based on death certificates, non-fatal MI: 2 of 3 criteria (severe prolonged chest pain, changes detectable by ECG or enzyme changes) | ≥70 g/day daily or on most days | Current abstainer | Age, smoking years, social class (participants free of ischaemic heart disease at baseline) |
| Boffetta et al., 1990[31]     | M, 40-59 | US, 1959-72 | CPS II | 551/7698 | ICD-7: 420-422 | ≥6 drinks/day (FFQ) | Current abstainer | Age, smoking |
| Renaud et al., 1998 [32]      | M, 40-60 | France, 1978-1993 | Health examination at the Centre de Medicine Preventive de Nancy | 86/9385 | ICD-9: 410-414 | ≥77 g/day (based on daily consumption) | Current abstainer | Age, education, smoking, serum total cholesterol, systolic blood pressure, BMI |
| Maskarinec et al., 1998[33]   | M, W, 30+ | US, 1975-94 | Multiethnic cohort study, Hawaii | 12/308 | ICD-9: 410-414 | ≥43 drinks per week (based on usual amount and frequency) | Current abstainer | Age, ethnicity, smoking, BMI, education, |
| Gun et al., 2006[34]          | M, not reported | Australia, 1980-2001 | Health Watch (Petroleum-industry workers) | 30/1226 | ICD-9: 410-414 | ≥7 drinks per day (based on typical frequency and amount) | Current abstainer | Age, calendar year, smoking |
| Study                          | Gender, Age Range | Country, Period               | Study Design                                      | Incidence/Fatality | Mortality Rate | Alcohol Intake Requirement | Alcohol Intake Method | Current Abstainer | Additional Details |
|-------------------------------|-------------------|-------------------------------|--------------------------------------------------|--------------------|-----------------|-----------------------------|-----------------------|-------------------|--------------------|
| Bazzano et al., 2009[35]      | M, 40+            | China, 1991-2000              | China National Hypertension Survey Epidemiology Follow-up Study | 52/6389             | NDI)            | ≥63 g/day (based on number of drinks per month) | Determined by endpoint committee based on medical records, death certificates | Current abstainer | Age, BMI, BP, physical activity, smoking, diabetes, education, urban vs rural, living in North China (history of IHD excluded) |
| Sull et al., 2009[36]         | M, 55+            | South Korea, 1985-2005        | Kangwha Cohort Study                             | 2/182              | Mortality       | ≥72 g/day daily (based on frequency per year and typical amount) | Death certificate, ICD-10: I20-I25 | Current abstainer | Age, history of chronic disease, smoking, BMI, BP, education |
| Oliveira et al., 2009[37]     | M, 18+            | Portugal, 1999-2003           | Cardiology Department of 4 hospitals, Porto     | 186/284            | Morbidity       | ≥60 g/day (FFQ) | Morbidity, first AMI patients who survived four days after diagnosis | Current abstainer | Age, education, family history of MI, waist-to-hip ratio, smoking, total energy intake, leisure time physical activity |
| Ruidavets et al., 2010 (Northern Ireland)[38] | M, 50-59          | Northern Ireland, 1991-2004   | Prospective Epidemiological Study of Myocardial Infarction (PRIME) | 9/240              | Incidence       | ≥75 g/day average (based on usual weekly total intake) | Incidence (fatal + non-fatal events), defined as coronary death and non-fatal MI (established by medical committee based on detailed clinical information from hospital or GPs) | Current abstainer | Restricted age range, previous IHD (medically diagnosed or Rose questionnaire) excluded |
| Ruidavets et al., 2010 (France)[38] | M, 50-59          | France, 1991-2004             | Prospective Epidemiological Study of Myocardial Infarction (PRIME) | 33/1134            | Incidence       | ≥75 g/day average (based on usual weekly total intake) | Incidence (fatal + non-fatal events), defined as coronary death and non-fatal MI (established by medical committee based on detailed clinical information from hospital or GPs) | Current abstainer | Restricted age range, previous IHD (medically diagnosed or Rose questionnaire) excluded |
| Study Details | Study Location | Sample Characteristics | Study Design | Total Number | Events | Event Definition | Current Abstainer | Follow-Up Characteristics |
|---------------|----------------|------------------------|--------------|--------------|--------|------------------|-------------------|--------------------------|
| Hvidfeldt et al., 2010 [39] | North America and Europe, 1974-1996 | M, W, 30-80 | Pooled analysis of 8 cohort studies | 105/2972 | Incidence (fatal + non-fatal events), ischaemic heart disease (standard criteria met in all individual studies) | ≥60 g/day (FFQ) | Current abstainer | Age, year of baseline, smoking, BMI, education, physical activity, energy intake, polysaturated fat, monosaturated fat, saturated fat, fiber, cholesterol intake, study origin (participants free of CVD, diabetes, cancers) |
| Yang et al., 2012 [40] | China, 1990-2005 | M, 40-79 | Nationwide cohort study | 123/20 586 | Mortality (based on death certificate), ICD-9: 410-414 | ≥60 g/day (based on typical weekly intake) | Current abstainer | Age, geographical area, participants with prior diseases at baseline were excluded |
| Romelsjö et al., 2012 [41] | Sweden, 1969-2004 | M, 18-20 | Swedish conscripts | 12/600⁰ | Incidence (fatal + non-fatal events), mortality (based on National Death Register and National Swedish inpatient register), ICD-9: 410 (MI) | >60 g/day (based on frequency and amount) | Current abstainer | Smoking, father (blue collar worker), divorced parents, runaway from home, truancy, low emotional control, low social maturity, IQ, health status, BMI |
| Sundby 1967 [42] | Norway, 1925-62 | M, 15+ | Ullevaal Hospital, Psychiatric Department, Oslo | 97/1716 | National Central Bureau of Statistics comparison to Oslo mortality statistics, ICD-7: ischaemic heart disease | Diagnosis of alcoholism | General population | Age- and sex-standardized |
| Schmidt & de Lint 1972 [43] | Canada, 1951-1964 | W, M, 15+ | Clinic of the Addiction Research Foundation, Toronto | 258/6478 | Death records in Ontario, other provinces, and some foreign countries, ICD-7: 420 ischaemic heart disease (253 cases), 422 myocardial degeneration (5 cases) | All patients with physical examination at entry for alcoholism treatment at specialized clinic | Ontario general population | Age- and sex-standardized |
| Source                          | Gender | Age | Country | Setting                                                   | Code | Diagnosis                        | Setting Description                                                                 |
|--------------------------------|--------|-----|---------|-----------------------------------------------------------|------|----------------------------------|-------------------------------------------------------------------------------------|
| Adelstein & White 1976 [44]    | W, M   | 15+ | UK      | 4 London Mental Hospitals, Mental Health Enquiry           | 137/2070 | ICD-8: 410-414                 | Inpatient treatment for alcoholism                                                   |
| Thorarinsson 1979 [45]         | M, 15+ |     | Iceland | National Psychiatric Register                             | 125/2863 | Death certificate, underlying cause, ICD-7: 420            | First admission to in- or out-patient institution                                    |
| Polich et al., 1981 [46]       | M, 18+ |     | US      | 8 of 44 NIAAA Alcoholism Treatment Centers                 | 24/755  | Underlying cause, ICD-8: 410-414 | Admission to specialized program for alcoholism                                      |
| Lindberg & Agren 1988 [47]     | W, M   | 15+ | Sweden  | Magnus Huss Clinic, Karolinska Hospital                   | 126/4543 | National Central Bureau of Statistics, underlying cause, ICD-8: 410-414 | First admission for alcoholism to specialized clinic                                |
| Denison et al., 1997 [48]      | M, 20+ |     | Sweden  | University Psychiatric Clinic, Lillhagen Hospital, Goeteborg | 25/1049 | Death certificate, underlying cause, ICD-9: 410-414       | Inpatients for detoxification, DSM-III-R criteria for alcohol dependence             |
| Noda et al., 2001 [49]         | M, 21-77|    | Japan   | All in or out-patient treatment facilities, Takatsuki City | 4/306  | Death certificate, underlying cause, ICD-9: 410-414       | Diagnosis of alcohol dependence/psychosis                                            |
| Haver et al., 2009 [50]        | W, 18+ |     | Sweden  | Early Treatment for Women with Alcohol Addiction (EWA) Unit, Karolinska Hospital | 10/420 | Swedish Causes of Death Register, ICD-8, ICD-9, and ICD-10: ischaemic heart disease | First admission for alcohol treatment (second sample 96% met DSM-III-R criteria for alcohol dependence) |
| Saieva et al., 2012 [51]       | W, M   | 16-94| Italy   | Alcohol Centre treatment                                   | 30/2272 | Regional Mortality Register, ICD-9: 410-414               | Physician diagnosis alcohol dependence (ICD-9)                                     |

**Abbreviations:** AMI, acute myocardial infarction; AUD, Alcohol use disorder; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; EPIC, European Prospective Investigation into Cancer and Nutrition; FFQ, food frequency questionnaire; ICDA, International Classification of Diseases, Adapted for Use in the United States; IHD, ischaemic heart disease; M, men only; MI, myocardial infarction; MONICA, Monitoring Trends and Determinants in Cardiovascular Disease; NHANES, National Health and Nutrition Examination Survey; PRIME, Prospective Epidemiological Study of Myocardial Infarction; SES, socio-economic status; SHEEP, Stockholm Heart Epidemiology Program; W, women only; WHO, World Health organization. ICD codes were included were reported.

*a Estimated.
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Supplementary material

Supplementary Methods
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Supplementary Tables
Supplementary Table 1. Characteristics of 34 Studies for Ischaemic Heart Disease in Heavy Drinkers, 1967-2012
Supplementary Methods

Systematic Review Protocol

Title: Systematic review and meta-analysis of heavy drinking and ischaemic heart disease

Protocol Information

Dates
All searches were conducted in week 4 of March 2014.

Stage
Review completed in April 2014.
Current stage: Meta-analysis completed.

Collaborators
None.

Review Methods

Review questions
What is the relative risk for ischaemic heart disease among heavy drinkers?

Context
Specific risk of chronic heavy drinking for ischaemic heart disease (IHD) in comparison to lifetime abstainers has not been systematically examined before and it is currently unclear whether chronic heavy drinking has a protective, neutral, or detrimental association with IHD. Population studies often miss many chronic heavy drinkers in order to maximize follow-up or because of other sampling issues [1]. Inadvertently, these samples mostly contain more favorable drinking behavior, such as low and regular alcohol consumption within a certain stratum of the socioeconomic continuum in high income countries. However, as is increasingly evident in middle income countries, this is not the drinking pattern observed globally [2]. Among participants missed in typical cohort studies is a subgroup of chronic heavy drinkers, namely people with alcohol use disorders (AUD), who drink on average considerably more than our threshold for heavy drinking [3 4].

Condition or domain
Ischaemic heart disease (morbidity or mortality).

Primary outcomes
Incidence of IHD events.

Secondary outcomes
Fatal and non-fatal IHD events.

Intervention/exposure
Chronic heavy drinking is the exposure of interest.

**Comparators/controls**
Standardized mortality rates compared to the general population or measure of relative risk in comparison to abstainers (current or lifetime).

**Types of studies to be included initially**
Observational studies (historical or prospective cohort and case-control studies).

**Literature searches**
Using PRISMA and MOOSE guidelines [5 6], we conducted two systematic searches using electronic databases from their inception (clinical samples) or 1980 (population samples) to fourth week of March 2014 for original articles, excluding letters, editorials, conference abstracts, reviews, and comments for variations of search terms for the exposure (alcohol consumption), outcome (IHD), and study design. Additionally, we hand searched references of identified papers and relevant reviews and meta-analyses.

**Participants/population**
Inclusion criteria: Adults (≥15 years) from population samples or clinical samples (patients with AUD in treatment), IHD was analyzed as a separate outcome (ICD-9: 410-414, ICD-10: I20-25), a measure of risk and its corresponding measure of variability was reported (or sufficient data to calculate these), and English-, German-, or Spanish-language.
Exclusion criteria: Adolescents (<15 years), population samples from people with IHD-related conditions. We excluded self-reported IHD outcomes, as well as studies reporting estimates on cardiovascular outcomes combined rather than IHD separately and studies with precursors as outcome.
Further inclusion criteria for population studies:
Case-control or prospective or historical cohort study design, exposure measurement had to cover a reference period of more than 2 weeks for average alcohol consumption at baseline.
Further inclusion criteria for clinical studies:
Prospective or historical cohort study design, mortality risk for diagnosed participants currently in AUD treatment (in- or out-patient, this includes DSM-III and IV ‘alcohol abuse and dependence’ and International Classification of Diseases [ICD-9 and 10] ‘harmful use’ or ‘non-dependent alcohol abuse’ and ‘alcohol dependence’) compared with the general population.

**Searches**

*Population samples*
Databases searched: MEDLINE, EMBASE, Web of Science (Science Citation Index Expanded, Social Sciences Citation Index, Arts & Humanities Citation Index), and ETOH (Alcohol and Alcohol Problems Science Database, National Institute on Alcohol Abuse and Alcoholism, January 1980–December 2003).
Search strategy in Medline (through OVID):
Clinical samples
Databases searched: MEDLINE, EMBASE, Web of Science (Science Citation Index Expanded, Social Sciences Citation Index, Arts & Humanities Citation Index), and ETOH (Alcohol and Alcohol Problems Science Database, National Institute on Alcohol Abuse and Alcoholism, January 1980–December 2003).
Search strategy in Medline (through OVID):

URL to search strategy
None.

Data extraction
From all relevant articles we extracted authors’ names, year of publication, country, calendar year(s) of baseline examination, follow-up period, setting, assessment of IHD and alcohol consumption or AUD diagnosis, mean and range of age at baseline, sex, number of observed IHD cases or deaths among participants by drinking group, number of total participants by drinking group, adjustment for potential confounders, and RR and its standard error. We used the most adjusted RR reported, and gave priority to estimates comparing heavy drinking to lifetime abstainers were abstracted by one reviewer. Full-text articles with uncertain eligibility were discussed by both authors until consensus was reached. To control for subjectivity, 10 papers were randomly selected and extracted by another author. No changes in abstraction were recorded. Primary
authors were not contacted by the authors in case there was not enough information presented in the article.

**Risk of bias**
Most quality scores are tailored for meta-analyses of randomized trials of interventions [7-10] and many criteria do not apply to epidemiological studies like the ones examined here. Also, their use in meta-analyses remains controversial [10 11]. Thus, quality assessment was incorporated differently by including quality components such as study design and alcohol measurement into the inclusion and exclusion criteria (please see also Data abstraction and Supplementary Table 1 for details). Quality checklists therefore would not have been able to distinguish the quality of selected studies in our analysis.

**Strategy for data synthesis**
Standardized mortality ratios (i.e. comparisons of mortality risks of patients in AUD treatment with the sex- and age-specific general population; see [12]), hazard ratios, odds ratios, and relative risks were treated as equivalent measures of risk. Analyses were stratified by sex where possible. If necessary, relative risks within studies were re-calculated based on the method described by Hamling et al. [13] and pooled across studies using inverse-variance weighted DerSimonian-Laird random-effect models to allow for between-study heterogeneity [14]. We quantified between-study heterogeneity using Cochran’s Q [15] and the \( I^2 \) statistic [16]. \( I^2 \) can be interpreted as the proportion of the total variation other than chance that is due to heterogeneity between studies. We tested for potential publication bias using Egger’s test [17]. Sensitivity analyses for the influence of single studies on the pooled relative risks were conducted omitting one study at a time and re-estimating the pooled relative risk. No change in conclusions was observed. All meta-analytical procedures were conducted on the natural log scale in Stata statistical software, version 12.1 (Stata Corp, College Station, Texas), and p<0.05 (two-sided) was considered statistically significant.

**Analysis of subgroups or subsets**
Subgroup analyses were completed for different classification of alcohol exposure (chronic heavy drinking based on average alcohol consumption and AUD patients in treatment), and for incidence, mortality,morbidity, and adjustment for confounders. Meta-regression was conducted to identify study characteristics (study design) that might influence the association between heavy drinking and IHD in all subgroups considered when more than 10 studies were available.

**Type of review**
Prognostic.

**Language**
English, Spanish, German.

**Country**
Canada.
Dissemination plans
Publication in peer-review journal.

Keywords
Heavy drinking, alcohol use disorder, heart disease, incidence, mortality, systematic review, meta-analysis

Details of any existing review of the same topic by the same authors
None.

Review status
Completed, but not published.
Supplementary Figure 1. Search Results for Population Studies on Chronic Heavy Alcohol Consumption and Ischaemic Heart Disease Risk

Articles identified:
- MEDLINE (n=1294)
- EMBASE (n=661)
- Web of Science (n=1258)
- Handsearch (n=2)

Unique articles (n=2769)

Excluded based on title or abstract with minimal uncertainty (n=2306)

Articles retrieved in full-text (n=463)

Articles excluded (n=449):
- Not case-control or cohort study design (n=21)
- No data for alcohol intake (n=198)
- IHD is not the outcome or self-reported (n=64)
- No data on chronic heavy drinking (n=135)
- Estimates not age-adjusted (n=1)
- Reference group is not lifetime abstainers (n=19)
- No deaths recorded (n=1)

Articles for quantitative analysis:
- Chronic heavy drinking (n=24)
- Lifetime abstainers are reference (n=11)
- Current abstainers are reference (n=13)
Supplementary Figure 2. Search Results for Patients with Alcohol Use Disorder (AUD, Clinical Samples) and Ischaemic Heart Diseases Mortality

Articles identified in search:
- MEDLINE (n=385)
- EMBASE (n=225)
- Web of Science (n=1123)
- Handsearch (n=6)

Unique articles (n=1608)

Excluded based on title or abstract with minimal uncertainty (n=1392)

Articles retrieved in full-text (n=216)

Articles excluded (n=206):
- Exposure not AUD (n=32)
- Not cohort study design (n=16)
- No control group (n=36)
- Not age-adjusted (n=5)
- Duplicate reports on the same study population (n=15)
- No cause-specific mortality (n=88)
- Not currently in AUD treatment (n=5)
- General population is not control group (n=2)
- IHD not reported (n=7)

Articles for quantitative analysis (n=10)
**Supplementary Figure 3.** Funnel Plot for Ischaemic Heart Disease Incidence among Chronic Heavy Drinkers with Lifetime Abstainers as the Reference Group

Effect size is log(RR)
Supplementary Figure 4. Funnel Plot for Ischaemic Heart Disease Incidence among Chronic Heavy Drinkers with Current Abstainers as the Reference Group.

Effect size is log(RR)
**Supplementary Table 1.** Characteristics of 34 Studies for Ischaemic Heart Disease Risk in Chronic Heavy Drinkers, 1967-2012

| Source                        | Sex, Age at baseline | Location, baseline period | Setting                                                                 | No. of heavy drinkers (IHD events/ total participants) | IHD assessment                                                                 | Heavy drinking definition                                                                 | Reference category                           | Adjustment                                                                 |
|-------------------------------|----------------------|---------------------------|--------------------------------------------------------------------------|--------------------------------------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------|----------------------------------------------------------------------------|
| Population samples            |                      |                           |                                                                          |                                                        |                                                                                 |                                                                                        |                                |                                                                            |
| Dyer et al., 1981[18]         | M, 40-55             | US, 1957-74              | Chicago Western Electric Company Study                                   | 12/78                                                  | Mortality, ischaemic heart disease (not defined)                                  | ≥77 g/day average (based on total intake per month)                                  | Lifetime abstainers             | Age (participants free of definite ischaemic heart disease)                |
| Kaufman et al., 1985[19]      | M, 30-55             | US, 1980-83              | Hospital-based, North eastern US (78 hospitals)                          | 209/299                                                | Morbidity, first MI (WHO criteria)                                                 | ≥67 g/day average (based on typical frequency and amount)                                | Lifetime abstainers             | Age (no history of MI or angina pectoris among controls)                  |
| Jackson et al., 1991[20]      | M, 25-64             | New Zealand, 1986        | Auckland                                                                | 33/68                                                  | Incidence (fatal and non-fatal events mortality and morbidity were reported separately), MONICA criteria | >81 g/day (based on typical frequency and amount last 3 months)                       | Lifetime abstainers             | Age, smoking, hypertension, social class, exercise, recent (12 months) change in drinking |
| Iso et al., 1995[21]          | M, 40-69             | Japan, 1975-87           | Ikawa, Honjo and Kyowa                                                  | 439/439                                                | Incidence (fatal + non-fatal events), WHO criteria for ischaemic heart disease (definite or suspected MI, angina pectoris, sudden death) | ≥70 g/day average (based on usual weekly intake)                                      | Lifetime abstainers             | Age, hypertension, serum total cholesterol, smoking, diabetes (history of ischaemic heart disease or stroke were excluded) |
| McElduff & Dobson 1997[22]    | M, 35-69             | Australia, 1983          | New South Wales (MONICA)                                                | 89/103                                                 | Incidence (fatal + non-fatal events), definite MI, possible MI, or coronary        | ≥90 g/day typical amount per drinking day on 5-6 days per week or daily                | Lifetime abstainers             | Age, smoking, BP, cholesterol, angina, stroke, MI, diabetes               |
| Reference                  | Gender | Age (yr) | Location         | Study Population          | Incidence & Death Details                                                                 | Non-drinkers Details                                                                 | Lifetime Abstainers | Additional Details |
|----------------------------|--------|----------|------------------|----------------------------|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|---------------------|--------------------|
| Rehm et al., 1997[23]      | M, 40-75 | US, 1971-87 | NHANES I         | Incidence (fatal + non-fatal events), ICD-9: 410-414 based on death certificate or hospital discharge diagnosis. Life & non-drinker ≥72 g/day (based on typical frequency and amount). | Lifetime abstainers | Age |
| Kitamura et al., 1998[24]  | M, 40-59 | Japan, 1975-93 | Osaka            | Incidence (fatal + non-fatal events) based on death certificates, absenteeism reports, insurance claims, and annual risk factor surveys; for all cases medical records were reviewed. Ischaemic heart disease (WHO criteria). Life & non-drinker ≥69 g/day (based on usual weekly intake). | Lifetime abstainers | Age, serum total cholesterol, smoking, BMI, left ventricular hypertrophy, history of diabetes |
| Klatsky et al., 2003[25]   | M, W, 18+ | US, 1978-98 | Kaiser Permanente, California | Mortality, ICD-9: 410-414 from death certificates. Life & non-drinker ≥6 drinks daily (FFQ). | Lifetime abstainers | Age |
| Romelsjö et al., 2003[26]  | M, 45-70 | Sweden, 1992-94 | Stockholm Heart Epidemiology Program (SHEEP) | Incidence (fatal + non-fatal events), morbidity was reported separately, (all first MI, based on death certificate, autopsy findings, or medical records). Life & non-drinker ≥70 g/day average (based on frequency in previous year and typical amount). | Lifetime abstainers | Age |
| Inoue et al., 2012[27]     | M, 35-101 | Japan, 1988-2006 | Pooled analysis of 6 large cohort studies in Japan | Mortality based on death certificates, ICD-10: I20-25 Life & non-drinker ≥69 g/day average (based on frequency and amount). | Lifetime abstainers | Age |
| Bergmann et al., 2013[28]  | M, 25-70 | Europe (23 centres in 10) | EPIC | Mortality (record linkage with death Life & non-drinker >60 g/day (based on amount per week). | Lifetime abstainers | Stratified by age and centre; adjusted for BMI, height, |
Current abstainers are the reference group

| Study                        | Gender | Age (yr) | Year | Cohort                          | N (cases)/N (controls) | Outcome Measures                                                                 | Current abstainer | Age Measure                                                                 |
|------------------------------|--------|----------|------|---------------------------------|------------------------|--------------------------------------------------------------------------------|-------------------|---------------------------------------------------------------------------|
| Friedman & Kimball, 1986[29] | M, F   | 30-59    | 1948-72 | Framingham Heart Study, Massachusetts | 15/138                | Mortality, ischaemic heart disease (not defined) Incidence (fatal + non-fatal events), ICD-9: 410-414, based on death certificates, non-fatal MI: 2 of 3 criteria (severe prolonged chest pain, changes detectable by ECG or enzyme changes) | Current abstainer | Age (all participants free of ischaemic heart disease at baseline)           |
| Shaper et al., 1987[30]    | M, F   | 40-59    | 1978-85 | British Regional Heart study     | 22/631                | >70 g/day daily or on most days                                                   | Current abstainer | Age, smoking years, social class(participants free of ischaemic heart disease at baseline) |
| Boffetta et al., 1990[31]  | M, F   | 40-59    | 1959-72 | CPS II                          | 551/7698              | ≥6 drinks/day (FFQ)                                                              | Current abstainer | Age, smoking                                                               |
| Renaud et al., 1998[32]    | M, F   | 40-60    | 1978-1993 | Health examination at the Centre de Medicine Preventive de Nancy | 86/9385                | ≥77 g/day (based on daily consumption)                                           | Current abstainer | Age, education, smoking, serum total cholesterol, systolic blood pressure, BMI |
| Maskarinec et al., 1998[33] | M, W   | 30+      | 1975-94 | Multiethnic cohort study, Hawaii  | 12/308                | ≥43 drinks per week (based on usual amount and frequency)                       | Current abstainer | Age, ethnicity, smoking, BMI, education,                                        |
| Gun et al., 2006[34]       | M, not reported | Australia, 1980-2001 | Health Watch (Petroleum-industry workers) | 30/1226a               | ≥7 drinks per day (based on typical frequency and amount)                        | Current abstainer | Age, calendar year, smoking                                               |

In the study by Fried & Kimball (1986), the current abstainers were the reference group. The study included both men and women aged 30-59 years, with a follow-up period from 1948 to 1972, using Framingham Heart Study data from Massachusetts. The outcome measures included mortality due to ischaemic heart disease, incidence of fatal and non-fatal events, based on death certificates and non-fatal MI criteria. The current abstainers were compared to the age group, with an age measure of all participants free of ischaemic heart disease at baseline.

In the study by Shaper et al. (1987), the current abstainers were also the reference group. The study included men and women aged 40-59 years, with a follow-up period from 1978 to 1985, using British Regional Heart Study data. The outcome measures included mortality, incidence of fatal and non-fatal events, based on death certificates and non-fatal MI criteria. The current abstainers were compared to the age, smoking years, and social class measures.

In the study by Boffetta et al. (1990), the current abstainers were the reference group. The study included men and women aged 40-59 years, with a follow-up period from 1959 to 1972, using CPS II data. The outcome measures included mortality based on death certificates, with an age measure of all participants.

In the study by Renaud et al. (1998), the current abstainers were the reference group. The study included men and women aged 40-60 years, with a follow-up period from 1978 to 1993, using data from the Centre de Medicine Preventive de Nancy. The outcome measures included mortality based on death information from physicians, with an age measure of all participants and smoking years.

In the study by Maskarinec et al. (1998), the current abstainers were the reference group. The study included men and women aged 30+, with a follow-up period from 1975 to 1994, using Multiethnic cohort study data. The outcome measures included mortality based on mortality files, with an age measure of all participants and smoking years.

In the study by Gun et al. (2006), the current abstainers were the reference group. The study included men, with a follow-up period from 1980 to 2001, using Health Watch data. The outcome measures included mortality based on death register, with an age measure of all participants and calendar year.

The studies used various outcome measures, including mortality, incidence of fatal and non-fatal events, based on death certificates and non-fatal MI criteria. The comparison was made between the current abstainers and other groups, with age measures varying from all participants free of ischaemic heart disease at baseline to smoking years and social class.
| Study                        | Gender | Age | Country | Study Details                                                                 | Incidence (fatal + non-fatal events) | Mortality | Mortality Definition | Mortality Source | Current Abstainer | Other Details                                                                 |
|------------------------------|--------|-----|---------|--------------------------------------------------------------------------------|--------------------------------------|-----------|----------------------|------------------|-------------------|-----------------------------------------------------------------------------|
| Bazzano et al., 2009[35]     | M, 40+ | China, 1991-2000 | China National Hypertension Survey Epidemiology Follow-up Study | 52/6389                             | ≥63 g/day (based on number of drinks per month) | Current abstainer | Age, BMI, BP, physical activity, smoking, diabetes, education, urban vs rural, living in North China (history of IHD excluded) |
| Sull et al., 2009[36]         | M, 55+ | South Korea, 1985-2005 | Kangwha Cohort Study | 2/182                              | ≥72 g/day daily (based on frequency per year and typical amount) | Current abstainer | Age, history of chronic disease, smoking, BMI, BP, education                  |
| Oliveira et al., 2009[37]    | M, 18+ | Portugal, 1999-2003 | Cardiology Department of 4 hospitals, Porto | 186/284                            | ≥60 g/day (FFQ) | Current abstainer | Age, education, family history of MI, waist-to-hip ratio, smoking, total energy intake, leisure time physical activity |
| Ruidavets et al., 2010 (Northern Ireland)[38] | M, 50-59 | Northern Ireland, 1991-2004 | Prospective Epidemiological Study of Myocardial Infarction (PRIME) | 9/240                              | ≥75 g/day average (based on usual weekly total intake) | Current abstainer | Restricted age range, previous IHD (medically diagnosed or Rose questionnaire) excluded |
| Ruidavets et al., 2010 (France)[38] | M, 50-59 | France, 1991-2004 | Prospective Epidemiological Study of Myocardial Infarction (PRIME) | 33/1134                           | ≥75 g/day average (based on usual weekly total intake) | Current abstainer | Restricted age range, previous IHD (medically diagnosed or Rose questionnaire) excluded |
| Study Reference | Gender, Age (Years) | Location, Time Period | Study Design | Incidence (fatal + non-fatal events) | Current Abstainer Criteria | Other Variables |
|-----------------|---------------------|-----------------------|--------------|--------------------------------------|-----------------------------|----------------|
| Hvidfeldt et al., 2010[39] | M, W, 30-80 | North America and Europe, 1974-1996 | Pooled analysis of 8 cohort studies | Incidence (fatal + non-fatal events), ischaemic heart disease (standard criteria met in all individual studies) | ≥60 g/day (FFQ) | Age, year of baseline, smoking, BMI, education, physical activity, energy intake, polysaturated fat, monosaturated fat, saturated fat, fiber, cholesterol intake, study origin (participants free of CVD, diabetes, cancers) |
| Yang et al., 2012[40] | M, 40-79 | China, 1990-2005 | Nationwide cohort study | Mortality (based on death certificate), ICD-9: 410-414 | ≥60 g/day (based on typical weekly intake) | Current abstainer |
| Romelsjö et al., 2012[41] | M, 18-20 | Sweden, 1969-2004 | Swedish conscripts | Incidence (fatal + non-fatal events), mortality (based on National Death Register and National Swedish inpatient register), ICD-9: 410 (MI) | >60 g/day (based on frequency and amount) | Current abstainer |
| Sundby 1967[42] | M, 15+ | Norway, 1925-62 | Ulleval Hospital, Psychiatric Department, Oslo | | | Age- and sex-standardized |
| Schmidt & de Lint 1972[43] | W, M, 15+ | Canada, 1951-1964 | Clinic of the Addiction Research Foundation, Toronto | | | Age- and sex-standardized |
| Reference       | Gender | Age Range | Country | Setting | Sample Size | Diagnosis/Definition | Population | Standardization |
|-----------------|--------|-----------|---------|---------|-------------|----------------------|------------|-----------------|
| Adelstein & White 1976 [44] | W, M | 15+ | UK, 1953-1974 | 4 London Mental Hospitals, Mental Health Enquiry | 137/2070 | ICD-8: 410-414 | Inpatient treatment for alcoholism | General population | Age- and sex-standardization |
| Thorarinsson 1979 [45] | M | 15+ | Iceland, 1951-1974 | National Psychiatric Register | 125/2863 | Death certificate, underlying cause, ICD-7: 420 | First admission to in- or out-patient institution | General population | Age-standardized |
| Polich et al., 1981 [46] | M | 18+ | US, 1973-77 | 8 of 44 NIAAA Alcoholism Treatment Centers | 24/755 | Underlying cause, ICDA-8: 410-414 | Admission to specialized program for alcoholism | General population | Age-, sex-, and race-standardized |
| Lindberg & Agren 1988 [47] | W, M | 15+ | Sweden, 1969-1983 | Magnus Huss Clinic, Karolinska Hospital | 126/4543 | National Central Bureau of Statistics, underlying cause, ICD-8: 410-414 | First admission for alcoholism to specialized clinic | General population | Age-and sex-standardized |
| Denison et al., 1997 [48] | M | 20+ | Sweden, 1986-1991 | University Psychiatric Clinic, Lillhagen Hospital, Goeteborg | 25/1049 | Death certificate, underlying cause, ICD-8: 410-414 | Inpatients for detoxification, DSM-III-R criteria for alcohol dependence | General population | Age, calendar year, and length of follow-up |
| Noda et al., 2001 [49] | M | 21-77 | Japan, 1972-92 | All in or out-patient treatment facilities, Takatsuki City Early Treatment for Women with Alcohol Addiction (EWA) Unit, Karolinska Hospital | 4/306 | Death certificate, underlying cause, ICD-9: 410-414 | Diagnosis of alcohol dependence/psychosis | General population | Age- and time period standardization |
| Haver et al., 2009 [50] | W | 18+ | Sweden, 1981-2007 | Swedish Causes of Death Register, ICD-8, ICD-9, and ICD-10: ischaemic heart disease | 10/420 | Swedish Causes of Death Register | First admission for alcohol treatment (second sample 96% met DSM-III-R criteria for alcohol dependence) | General population | Matched on year of birth, marital status, SES, education |
| Saieva et al., 2012 [51] | W, M | 16-94 | Italy, 1985-2006 | Alcohol Centre treatment | 30/2272 | Regional Mortality Register, ICD-9: 410-414 | Physician diagnosis alcohol dependence (ICD-9) | General population | Age- and sex-standardized |

Abbreviations: AMI, acute myocardial infarction; AUD, Alcohol use disorder; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; EPIC, European Prospective Investigation into Cancer and Nutrition; FFQ, food frequency questionnaire; ICDA, International Classification of Diseases, Adapted for Use in the United States ; IHD, ischaemic heart disease; M, men only; MI, myocardial infarction; MONICA, Monitoring Trends and Determinants in Cardiovascular Disease; NHANES, National Health and Nutrition Examination Survey; PRIME, Prospective Epidemiological Study of Myocardial Infarction; SES, socio-economic status; SHEEP, Stockholm Heart Epidemiology Program; W, women only; WHO, World Health organization. ICD codes were included were reported.

a Estimated.
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