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Meta- and Pooled Analyses

Irregular Heavy Drinking Occasions and Risk of Ischemic Heart Disease: A Systematic Review and Meta-Analysis

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Contrary to a cardioprotective effect of moderate regular alcohol consumption, accumulating evidence points to a detrimental effect of irregular heavy drinking occasions (>60 g of pure alcohol or ≥5 drinks per occasion at least monthly) on ischemic heart disease risk, even for drinkers whose average consumption is moderate. The authors systematically searched electronic databases from 1980 to 2009 for case-control or cohort studies examining the association of irregular heavy drinking occasions with ischemic heart disease risk. Studies were included if they reported either a relative risk estimate for intoxication or frequency of ≥5 drinks stratified by or adjusted for total average alcohol consumption. The search identified 14 studies (including 31 risk estimates) containing 4,718 ischemic heart disease events (morbidity and mortality). Using a standardized protocol, the authors extracted relative risk estimates and their variance, in addition to study characteristics. In a random-effects model, the pooled relative risk of irregular heavy drinking occasions compared with regular moderate drinking was 1.45 (95% confidence interval: 1.24, 1.70), with significant between-study heterogeneity ($I^2 = 53.9\%$). Results were robust in several sensitivity analyses. The authors concluded that the cardioprotective effect of moderate alcohol consumption disappears when, on average, light to moderate drinking is mixed with irregular heavy drinking occasions.

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

Abbreviations: CI, confidence interval; IHD, ischemic heart disease; RR, relative risk.

Alcohol consumption is causally related to some 100 diseases and conditions and has been found to be one of the most important risk factors for burden of disease worldwide, especially in developed countries (1). One of the most important disease outcomes causally related to alcohol is ischemic heart disease (IHD), the most common cause of death in many countries, with growing importance from a global perspective (2). However, the relation between alcohol consumption and IHD is complex. Although regular light to moderate consumption has been linked to beneficial effects on IHD (3) by good epidemiologic evidence and plausible underlying pathways (4, 5), the impact of heavy drinking occasions is less clear. It has been especially doubtful whether, on average, light to moderate drinking mixed with occasional heavy drinking would result in a cardioprotective effect, a detrimental effect, or no effect in comparison to either moderate drinking or abstention. The answer to this question is further complicated because the concept of irregular binge or heavy drinking is not uniformly defined (4, 6).

A recent meta-analysis (7) of 6 studies aimed to summarize the evidence for an effect of irregular heavy drinking compared with abstention, with a pooled relative risk estimate of 1.10 (95% confidence interval (CI): 1.03, 1.17). Although this analysis was an important step forward, we identified more studies that could provide data suitable for an investigation of irregular heavy drinking occasions and also interpreted findings of some studies differently.

Specifically, our objective was to test whether the risk of irregular heavy drinking episodes was different compared with regular moderate drinking at comparable levels of average alcohol intake. The answer to this question has

important consequences for prevention, including low-risk drinking guidelines, which typically include recommendations on maximal drinks per occasion. We conducted a systematic review of the literature and used random-effects meta-regression to quantify evidence for an effect of irregular heavy drinking occasions among drinkers of as much as 60 g of pure alcohol per day on average, corresponding to about 5 standard drinks (12 g of pure ethanol) per day. Beyond this point, the effect of irregular heavy drinking episodes cannot be distinguished from regular heavy drinking with the common 5- or- more measure for heavy episodic drinking.

MATERIALS AND METHODS

Search strategy

We systematically searched for potentially relevant original papers using the following electronic databases from January 1980 to the first week of July 2008: MEDLINE, EMBASE, Web of Science (Science Citation Index Expanded, Social Sciences Citation Index, Arts & Humanities Citation Index), ETOH (Alcohol and Alcohol Problems Science Database, National Institute on Alcohol Abuse and Alcoholism, January 1980–December 2003), and AIM (Alcohol in Moderation, alcohol industry database). Additionally, we hand searched references of identified papers and relevant reviews (4, 8–19) and meta-analyses (3, 7, 20–23). Because of resource limitations, we did not include ''gray literature'' in our search. The search was updated to December 2008, with no changes.

Because the concept of heavy drinking episodes is not clearly defined, we used broad search criteria and the following keywords and subject headings to identify relevant articles in electronic databases: (alcohol or ethanol) AND (heavy drinking occasion* or heavy episodic drinking or binge drinking or alcoholic intoxication or problem drinking or hangover* or irregular or pattern* or inebriation) AND (coronary heart disease or coronary artery disease or ischemic heart disease or ischaemic heart disease or myocardial infarction or sudden cardiac death or angina pectoris or coronary death) AND (case or cohort or ratio or risk* or prospective* or follow*). No language restrictions were applied. Eligible were original publications (we excluded letters, editorials, conference abstracts, reviews, and comments) of case-control and cohort studies reporting incidence, hazard ratios, relative risks, or odds ratios of heavy drinking episodes ($\geq$60 g of pure alcohol per occasion, or $\geq$5 standard drinks (about 12 g of pure ethanol) per occasion) or intoxication in comparison to drinkers with no heavy drinking episodes. Therefore, we included studies reporting a measure of heavy drinking episodes either stratified by frequency of drinking days per week or adjusted for average total alcohol intake. However, we excluded regular heavy drinkers (>60 g/day) and qualitative characterizations of alcohol exposure, such as ''problem drinkers.'' Cohort studies were included if they measured alcohol intake at baseline among IHD-free participants and prospectively assessed incidence of IHD. Endpoints were determined by standard World Health Organization criteria (24–26).

We excluded self-reported IHD morbidity, as well as studies reporting estimates on cardiovascular outcomes combined rather than IHD separately and studies with precursors as an outcome. One author (M. R.) performed the search and excluded studies at the first exclusion pass. Studies identified for a more detailed assessment (those that reported any measure of heavy drinking and IHD as an outcome) were discussed and agreed upon by both authors without blinding of study characteristics. Studies failing to meet the full inclusion criteria that contained relevant information on the objective were included as indirect evidence.

Data extraction

Because IHD is a rare outcome, hazard ratios, odds ratios, or relative risks were treated as equivalent measures of risk. In case the reference category was not a corresponding non-heavy-drinking group but, for example, abstainers, we recalculated the effect size measure to derive a comparison of heavy drinking episodes with non-heavy-drinking episodes as the reference category either in comparable strata of average total alcohol intake or adjusted for total alcohol intake. Irregular heavy drinking occasions were defined as 60 g or more per day at least 12 times per year but not more than 5 days per week. Thus, we excluded rare and regular heavy drinkers (>60 g/day on average). In cases where no confidence interval, standard error, or variance for a risk estimate was reported, we estimated the corresponding standard error from the raw numbers of cases and controls (or persons at risk) (27, 28). We abstracted information on study design, endpoint, exposure assessment, and adjustment for confounders. We used maximally adjusted risk estimates where possible; however, we avoided estimates adjusted for blood pressure and cholesterol because these risk factors represent a mediator on the causal pathway rather than confounders (4, 29, 30), resulting in an underestimate of the true relation. Where possible, we used estimates excluding former drinkers and occasional drinkers (<12 drinking occasions per year).

Data synthesis

To be included in the quantitative analysis, studies had to provide sufficient data to calculate an effect-size measure and its corresponding measure of variability. Because we abstracted multiple estimates from several studies, we prepooled relative risks to derive one overall relative risk for each study using fixed-effects estimates weighted by the inverse of their variance. All analyses were performed on the natural log scale. Because of the widely different methodological approaches used to examine heavy drinking occasions in the individual studies, we used DerSimonian-Laird random-effects models (31) to derive a pooled effect across studies, in which the between-study variance is estimated in addition to the specified within-variance component. Using the *metan* (32) and *metareg* command in Stata software (Stata Corporation, College Station, Texas), we investigated potential sources of heterogeneity on the study level and their influence on the pooled effect size using

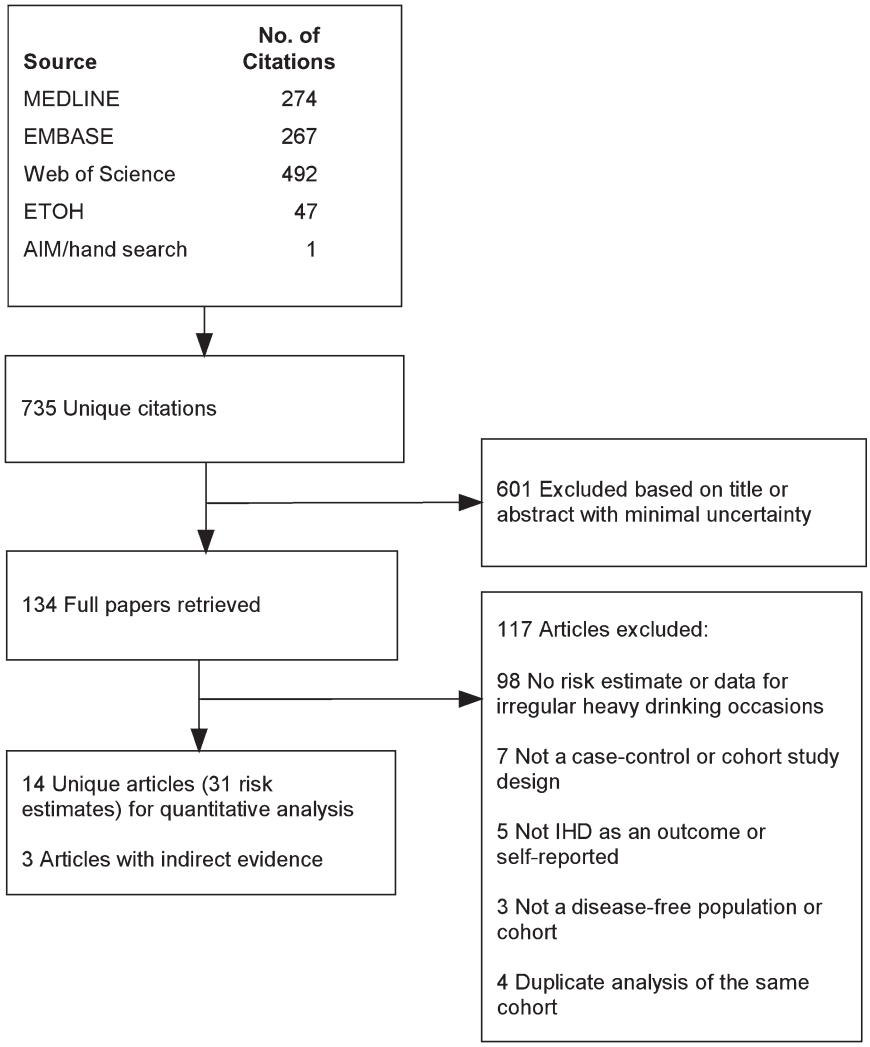

Figure 1. Flowchart of the meta-analysis search strategy and process of selecting papers on irregular heavy drinking occasions and risk of ischemic heart disease. AIM, Alcohol in Moderation; ETOH, Alcohol and Alcohol Problems Science Database; IHD, ischemic heart disease.

random-effects meta-regression models. We examined heterogeneity using Cochrane's Q-test (33) and the I^2 statistic (34). I^2 can be interpreted as the proportion of the total variation in the estimated slopes for each study due to heterogeneity between studies (34).

Presence and influence of small-study effects were explored by using the test described by Peters et al. (35), a linear regression of the log-transformed effect estimates on the reciprocal of the total sample size, weighted by a function of the sample size. The final data set for analysis included the log-relative risk and corresponding standard error, study ID, and dummy variables depicting study design (cohort vs. case-control), adjustment for age only, adjustment for smoking, and an indicator representing risk estimates for 9 or more drinks per occasion. Analyses were conducted with Stata version 10.1 software (36). A multilevel meta-regression model using robust standard errors in a variance-known model in HLM statistical software, version 6 (37, 38), was used to replicate the main analysis and investigate a potential dose-response relation by including a dummy variable representing 9 or more drinks per irregular heavy drinking occasion on the within-study level.

RESULTS

Search results

The electronic search revealed 1,081 citations (Figure 1). After removal of duplicates, 734 unique references were screened for inclusion. Of those, based on title and abstract, 134 full papers were obtained and were checked for inclusion. In total, 14 unique articles (39–52) that met the inclusion criteria for the quantitative part were identified; of those, 10 were cohort studies and 4 were case-control studies. Three additional papers with indirect evidence were identified (53–55).

Tables 1 and 2 show characteristics of studies included in the quantitative part of the meta-analysis. Of the 14 articles

Table 1. Characteristics of 10 Cohort Studies Selected for Quantitative Analysis of the Effect of Irregular Heavy Drinking Occasions on Ischemic Heart Disease Risk

Study (Reference No.), Year	Outcome	Alcohol Measurement	Sex	Incident No. of IHD Cases, Irregular Heavy Drinking/Non-heavy Drinking	Average Daily Alcohol Intake (Where Applicable)	Heavy Drinking Episode	Reference Category	Follow-up Time, Years	Age, Years	Country	Adjustment
Tolstrup et al. (49), 2006	Morbidity (hospital discharge register) and mortality (cause of death register) (ICD-8 codes 410–414, ICD-10 codes I20–I25)	Typical drinking dose (1 standard drink = 12 g of ethanol)	W	9/52	7–13 days/week	≤1 day/week	5–7 days/week	5.7	50–65	Denmark	Age; education; smoking; physical activity; BMI; total intake of vegetables, fruit, fish, and saturated fat
			M	31/90	7–13 days/week	≤1 day/week	5–7 days/week				
			M	52/90	14–20 days/week	≤1 day/week	5–7 days/week				
			M	8/90	14–20 days/week	2–4 days/week	5–7 days/week				
Mäkelä et al. (43), 2005	Morbidity (hospital discharge register) and mortality (cause of death register) (ICD-8 and ICD-9 codes 410–414, ICD-10 codes I20–I25)	Drinking episode leading to BAC >0.1% (HED)	W	4/18		HED only	Mostly non-HED	14.4	25–69	Finland	Age, total alcohol intake, period, marital status, education, smoking
			M	55/25		HED only	Mostly non-HED				
Laatikainen et al. (42), 2003	Mortality (cause of death register) (ICD-9 codes 410–414, ICD-10 codes I20–I25)	Any heavy drinking episode (1 standard drink = 12 g of ethanol)	M	38/85		Any ≥6 drinks per beverage type in the past year	≤5 drinks per beverage type in the past year	5 years and 10 years	25–64	Finland	Age (continuous), average alcohol intake (g/week: 0–95.9, 96–199.9, ≥200), smoking (current vs. other), education (low, medium, high)
Mukamal et al. (51), 2003	Fatal and nonfatal MI (WHO criteria (26))	Drinking frequency within narrow categories of average total alcohol intake	M	173 combined	10–14.9 g	<3 drinking days	≥3 drinking days	12	40–75	United States	Age, smoking (6 categories)
			M	193 combined	15–29.9 g	<3 drinking days	≥3 drinking days				

			M	139 combined	30–49.9 g	<3 drinking days	≥3 drinking days				
Murray et al. (48), 2002	Morbidity and mortality (physician visits, hospital stays and vital statistics files, ICD-9-CM codes 410–414)	Any heavy drinking episode (1 standard drink = 13 g of ethanol)	M	59 combined		Any ≥8 drinks per occasion in the past year	None in the past year	8	18–64	Canada	Age, total alcohol intake (g/day: 0.65–5.77, 5.78–18.1, >18.1), education, marital status, smoking
Malyutina et al. (44), 2002	Mortality (death register, autopsy reports, MONICA register, ICD-9 codes 410–414)	Typical drinking dose (information provided in grams)	M	133/87		80–120 g/drinking day	<80 g/drinking day	9.5	25–64	Russia	Age only
				70/87		120–160 g/drinking day	<80 g/drinking day				
				36/87		>160 g/drinking day	<80 g/drinking day				
Kauhanen et al. (46), 1997	Fatal MI (WHO MONICA criteria (25))	Typical drinking dose (beer drinkers only)	M	6/22		≥6 drinks per occasion	≤6 drinks per occasion	5.6	42–60	Finland	Age, total alcohol consumption
Shaper et al. (50), 1987	Morbidity (2 of 3 standard criteria: severe prolonged chest pain, electrocardiographic or enzyme changes, and mortality (death certificate))	Typical drinking dose (1 standard drink = 8 g of ethanol)	M	24/20	20–40 drinks/week	>6 drinks on weekends	3–6 drinks daily or almost daily	6.2	40–59	United Kingdom	Age, years of smoking, social class
Poikolainen (52) 1983	Mortality (death certificate, ICD-7)	Intoxication	M	27 combined		Once weekly	None in the past year	12	39.1[a]	Finland	Age, marital status
Kozarevic et al. (39), 1982	Mortality (sudden and nonsudden CHD death, death certificate)	Inebriation	M	35/56		At least a month ago	Less than a month ago	7	35–62	Yugoslavia	None, but multivariate regression by area (including age, blood pressure, smoking, cholesterol level, frequency of drinking, and BMI as confounders) confirmed the relation for sudden CHD death

Abbreviations: BAC, blood alcohol content; BMI, body mass index; CHD, coronary heart disease; HED, heavy episodic drinking; ICD, *International Classification of Diseases*; M, men; MI, myocardial infarction; MONICA, Monitoring of Trends and Determinants in Cardiovascular Disease; W, women; WHO, World Health Organization.

[a] Median.

Table 2. Characteristics of 4 Case-Control Studies Selected for Quantitative Analysis of the Effect of Irregular Heavy Drinking Occasions on Ischemic Heart Disease Risk

Study (Reference No.), Year	Outcome	Alcohol Measurement	Sex	Incident No. of IHD Cases, Irregular Heavy Drinking/Non-heavy Drinking	Average Daily Alcohol Intake (Where Applicable)	Heavy Drinking Episode	Reference Category	Age, Years	Country	Adjustment
Dorn et al. (41), 2007	Nonfatal MI (WHO criteria (24))	Intoxication	W	10/108		At least once a month	Less than once a month	35–69	United States	Age (years), BMI, race, smoking, menopausal status
Kabagambe et al. (45), 2005	Nonfatal MI (WHO MONICA criteria (25))	Typical drinking dose (information provided in grams)	M	105/43[a]	10.0–14.9 g	Intake on 1–2 days/week	3–7 days/week	<75	Costa Rica	Age only
			M	73/22[a]	15.0–29.9 g	Intake on 1–2 days/week	6–7 days/week			
McElduff and Dobson (47), 1997	Morbidity and mortality (WHO MONICA criteria (25))	Typical drinking dose (1 standard drink = 10 g of ethanol)	W	5/143	<10 g/day	≥5 drinks on <1–4 days/week	1–4 drinks on <1–4 days/week	35–69	Australia	Age, smoking, blood pressure, cholesterol, angina, stroke, previous MI, diabetes
			W	13/61	10–20 g/day	≥5 drinks on 1–2 days/week	1–4 drinks on 3–7 days/week			
			W	2/18	20–40 g/day	≥5 drinks on 3–4 days/week	1–4 drinks on 5–7 days/week			
			M	32/533	<10 g/day	5–8 drinks on <1–4 days/week	1–4 drinks on <1–4 days/week			
			M	8/254	10–20 g/day	≥9 drinks on <1 days/week	1–4 drinks on 3–7 days/week			
			M	34/182	20–40 g/day	5–8 drinks on 3–4 days/week	1–4 drinks on 5–7 days/week			
			M	38/182	20–40 g/day	≥9 drinks on 1–2 days/week	1–4 drinks on 3–7 days/week			
Hammar et al. (40), 1997	Fatal (National Cause of Death register) and nonfatal (hospital discharge data) MI	Intoxication	W	17/121		At least ½ bottle of spirits or intoxication	Never intoxicated or ½ bottle of spirits	<75	Sweden	Age, region, year, smoking
			M	135/143		At least ½ bottle of spirits or intoxication	Never intoxicated or ½ bottle of spirits			

Abbreviations: BMI, body mass index; M, men; MI, myocardial infarction; MONICA, Monitoring of Trends and Determinants in Cardiovascular Disease; W, women; WHO, World Health Organization.
[a] Number of cases estimated based on information in the paper.

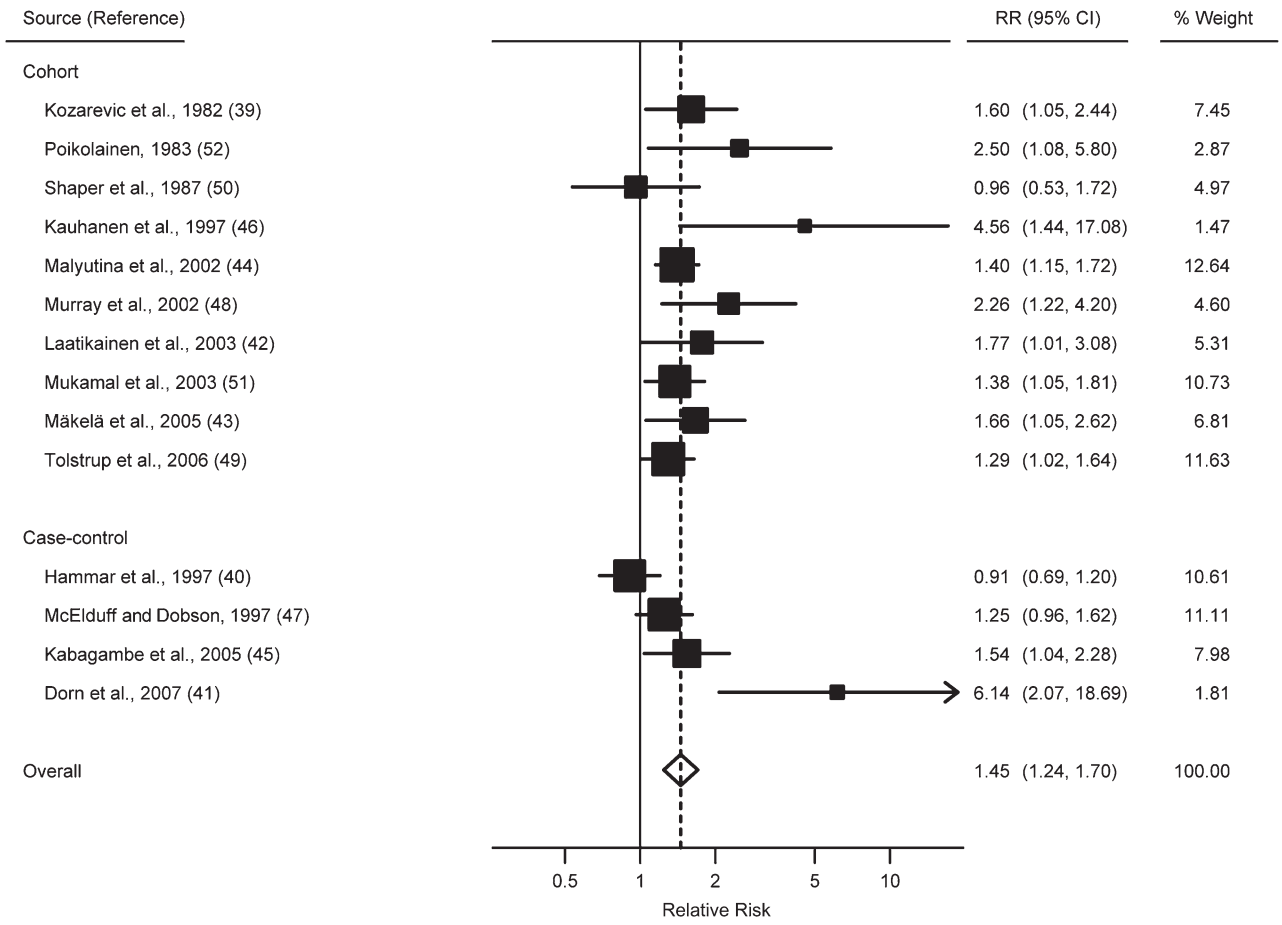

Figure 2. Forest plot of irregular heavy drinking occasions compared with regular moderate drinking and risk of ischemic heart disease. Weights are from random-effects analysis ($I^2 = 53.9\%$, $P = 0.008$). CI, confidence interval; RR, relative risk.

included in the quantitative analysis, 7 provided 1 risk estimate, 3 provided 2 estimates, 2 provided 3 estimates, and 1 each provided 4 estimates and 8 estimates. In addition to the quantitative measure of heavy drinking defined above, we accepted 4 studies (39–41, 43) with intoxication as the exposure measurement. Intoxication seemed to be a good proxy for the heavy drinking occasions. In some ways, given the tolerance associated with alcohol dependence, it is even a better measure for defining heavy drinking occasions, especially for people with, on average, light to moderate drinking. Adjustment for potential confounders differed across studies. One study (47) provided estimates adjusted for blood pressure, cholesterol, and diabetes—all potential mediators—but, because they were the only effect measures published, we included the estimate as well. This choice can be seen as conservative, because the true relation is underestimated. Eight studies used morbidity and mortality combined as the endpoint. Four studies were restricted to mortality and 2 to nonfatal events. A total of 2,171 incident IHD events and 3,475 controls among case-control studies and 1,637 events for 50,031 persons at risk among cohort studies were included in the quantitative analysis.

Meta-analysis

Prepooled and random-effects summary estimates are provided in Figure 2. Heavy irregular drinking occasions (>60 g of pure alcohol per occasion) were significantly associated with incidence of IHD morbidity and mortality compared with regular moderate drinking (pooled relative risk (RR) = 1.45, 95% CI: 1.24, 1.70). We detected significant, but moderate heterogeneity ($Q = 28.2$, $P = 0.008$; $\tau^2 = 0.029$, $I^2 = 53.9\%$). The pooled fixed-effects estimate (RR = 1.36, 95% CI: 1.24, 1.50) was slightly lower than the random-effects estimate. Inclusion of study design (case-control or cohort design) as an independent variable in a random-effects meta-regression model did not result in statistical significance ($P = 0.40$), neither did adjustment for smoking ($P = 0.37$) or adjustment for age only ($P = 0.42$). Repetition of these analyses in HLM software, taking into account the hierarchical structure of the data set simultaneously rather than in a 2-step procedure used in Stata software, revealed almost identical results (pooled random-effects RR = 1.43, 95% CI: 1.25, 1.64). We further tested a dummy variable representing 9 or more drinks per occasion on the within-study level (which depicts multiple

relative risk estimates within each study). The variable was not significant ($P = 0.20$) when entered into a meta-regression model.

We performed several sensitivity analyses to test the robustness of our findings. None of the studies had an excessive influence on the overall estimate. Reestimation of the random-effects models by omitting each study separately resulted in random variation around the overall estimate. In the study by Kozarevic et al. (39), exclusion of participants who reported never being inebriated (which includes mostly nondrinkers) yielded a risk estimate almost identical to the one calculated for this study. Visual inspection of the forest plot (Figure 2) suggests a relatively consistent effect when all studies are considered, with 2 outliers on each side of the pooled risk estimate. Peters et al.'s test (35) did not indicate presence of publication bias or small-study effects ($P = 0.24$). The respective intercept, representing the adjusted effect when publication bias is assumed to be present, corresponded to a relative risk of 1.28 (95% CI: 0.98, 1.66), slightly lower than the effects found in the meta-analyses.

Indirect evidence

Among the studies excluded from the quantitative analysis because they did not meet our inclusion criteria, we identified 3 providing indirect evidence. Although those studies did not report a risk estimate for heavy drinking occasions as defined above, they provided indirect evidence of an association of frequency of drinking days with IHD risk controlled for total alcohol consumption. Trevisan et al. (53), in their population-based case-control study of white men in the United States, reported a relative risk of 1.91 (95% CI: 1.21, 3.01) for weekend drinking versus all other drinking. In their cohort study, Harriss et al. (54) showed, based on drinking in the week before the baseline interview, a lower risk for male drinkers consuming alcohol on 3–5 days (RR = 0.49, 95% CI: 0.27, 0.87) and on 6–7 days (RR = 0.49, 95% CI: 0.26, 0.92) compared with drinkers reporting alcohol consumption on 1–2 days (RR = 0.74, 95% CI: 0.48, 1.23). A comparison of incident cases of myocardial infarction with population estimates from Switzerland showed that prevalence of heavy drinking occasions (6 or more drinks for women, 8 or more drinks for men) among myocardial infarction cases was twice as high as in the general population after age standardization for both less than monthly (20.7% vs. 10.9%) and monthly or more frequent heavy drinking occasions (6.8% vs. 3.4%) (55).

DISCUSSION

The 14 studies included in the quantitative part of this meta-analysis revealed a 45% risk increase for the effect of episodic heavy drinking occasions while controlling for volume of alcohol consumed. Indirect evidence supports the direction and size of those findings. Several limitations, specific both to our analysis and to research involving alcohol consumption and IHD risk in general, apply to this study. Heterogeneity was expected because of the vastly different methods used to identify or report relative risk estimates for irregular heavy drinking occasions within the individual studies. Indeed, reporting of methods and results was generally inconsistent across studies and in some cases made it difficult to interpret or recalculate reported risk estimates. We used a very conservative approach in determining comparability of risk estimates and consider our pooled relative risk most likely an underestimate because misclassification would have led to bias toward no risk in many studies. Even though we used one study reporting risk estimates including variables on the pathway between alcohol consumption and IHD, those estimates would attenuate an increased risk due to irregular heavy drinking occasions, especially because of the strong and almost linear positive relation of alcohol consumption with hypertension (4, 56, 57). None of the cohort studies included in our analysis assessed alcohol consumption more than once at baseline. While change in alcohol intake over time might be an important factor to consider (58, 59), the true effect of heavy drinking is probably underestimated because of regression dilution (60). Because we did not include an abstainer group in our analysis and used risk estimates that separated former drinkers from their analysis, it is unlikely that a sick-quitter effect (61, 62) influenced our findings.

We cannot exclude the possibility that study-specific factors modified our summary estimate; power to test such effects was limited because of the small number of studies included (63). Therefore, we restricted testing of qualitative study characteristics to 4 independent variables assessed separately in meta-regression models. None of those characteristics was statistically significant (see above). Although a dose-response relation seems plausible when assessing the results of McElduff and Dobson (47), we did not find supporting evidence for such a relation when combining all available study results. However, this must be seen in light of the relatively small number of studies explicitly measuring intake higher than 5 or more drinks. We refrained from testing other variables because of low statistical power.

Presence of heterogeneity is a problem for every statistical test for publication bias (35, 64, 65). Although we detected moderate heterogeneity as measured by I^2 (53.9%), between-study variance was relatively small ($\tau^2 = 0.029$). While Peters et al.'s test (35) did not indicate a small-study effect, low power, problems with statistical properties, and presence of at least some heterogeneity make cautious interpretation necessary. Even if publication bias was present, it seems to be small because fixed and random-effects estimates were similar in size and direction.

The results of our quantitative meta-analysis show the direction, size, and consistency of the effect of irregular heavy drinking occasions. Determining the strength of the evidence is, however, a judgment call. In the absence of large-scale, long-term, randomized studies because of ethical and practical reasons, we have to rely on evidence from short-term biomedical experimental research and observational studies. By pooling observational studies, we gain power and precision, but measurement error, selection bias, and confounding are inherent to our analysis, as they are to the individual studies, and need to be considered in determining the validity of any estimates derived from such study designs. A meta-analysis of observational studies always

leaves room for producing precise estimates of biased results.

Aside from observational studies, evidence from biochemical trials supports an effect of heavy drinking episodes on IHD risk. On the one hand, regular low to moderate alcohol intake has been found to have beneficial, dose-dependent effects on IHD, mainly by increasing high density lipoproteins, inhibiting platelet activation, reducing fibrinogen levels, and producing antiinflammatory effects (4, 5, 12). On the other hand, heavy drinking occasions have 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 drinking, as well as in subjects with existing coronary disease through silent myocardial ischemia and angina (4). Evidence for effects of irregular heavy drinking episodes on lipid profiles is somewhat inconsistent (66); a comprehensive review concluded that low density lipoproteins are increased by heavy drinking episodes, resulting in detrimental effects on the heart, in contrast to regular moderate drinking, which raises high density lipoprotein levels (30).

Although some form of cardioprotective effect of alcohol consumption is supported by many epidemiologic studies and short-term randomized controlled trials, findings from studies that seem to contradict a cardioprotective effect of moderate alcohol consumption on IHD might be explained by predominance of irregular heavy drinking occasions in the respective population or subpopulations included. For example, Sempos et al. (67) found no protective effect for African Americans when examining average alcohol intake and coronary heart disease among a representative sample in their cohort study. For people of white origin, however, a beneficial effect was evident, and the authors argued that it might be explained by the higher proportion of heavy drinking episodes among African Americans. Similar results have been found in another US study (68).

Ecologic studies, even though they are not suited to quantitatively summarizing the relation of alcohol and IHD risk, indicate that heavy drinking occasions might explain their findings. For some time, the apparent failure to detect any cardioprotective effects of alcohol consumption in studies from Russia and other Eastern European countries has been discussed. Examining death certificates in Moscow, Chenet et al. (69) detected an increase in cardiovascular deaths (especially sudden death) on Saturdays, Sundays, and Mondays among a relatively young population, in which one would not necessarily expect such causes of death. Similar weekly variations were reported for death from alcohol poisoning and alcohol-related violence, which are clearly linked to heavy drinking occasions. A parallel analysis revealed similar results in Lithuania (70). However, caveats pertaining to ecologic studies in general make cautious interpretation necessary. A misclassification of cause of death from acute alcohol intoxication, one potential alternative explanation, does not seem to explain the findings (71).

Another study from Scotland, where heavy drinking on the weekend is very common, also showed higher IHD mortality occurring outside the hospital on Mondays (72, 73). A comparison of average alcohol consumption and IHD in France and Northern Ireland showed a higher risk of IHD events in comparable quartiles of alcohol consumption in Northern Ireland (74). Again, heavy drinking on weekends is highly prevalent in Northern Ireland, whereas regular moderate consumption is more prevalent in France (75). Besides the effect of heavy drinking occasions on high density and low density lipoproteins, these studies, in addition to the study by Kozarevic et al. (39) included in our analysis, indicate that heavy drinking episodes may have a particular effect on sudden death (71, 76–81), whereas low to moderate alcohol consumption seems to protect especially against sudden cardiac death (79, 82, 83).

Several issues remain. Reviewing the evidence for potential explanations for the detrimental effect of alcohol on the heart in Eastern Europe, McKee and Britton (30) showed biologically plausible mechanisms for the specific effect on sudden cardiac death through increased risk of thrombosis, ventricular arrhythmia, and atrial fibrillation after cessation of drinking. However, the evidence is mostly indirect (30, 71, 76–81) or derives from observations among chronic alcohol users, for whom both acute intake and withdrawal have been associated with cardiac arrhythmia (4, 84–86). Suhonen et al. (77) found a significant increased risk of sudden death for nonsmokers but not for smokers in a cohort study in Finland, a typically irregular-heavy-drinking country. Wannamethee and Shaper (76) reported an increased risk of sudden death for regular heavy drinkers in the same cohort (50) we included in our analysis. High prevalence of sudden cardiac death in the United States (87) and elsewhere makes this an urgent topic for future research.

Considering all limitations, we found that results were relatively consistent across studies. Irregular heavy drinking occasions are associated with increased risk of IHD compared with moderate regular drinking. The diversity of study designs and of countries in which studies were conducted, in studies covering many decades, and with different assessments of heavy drinking occasions strengthen the conclusion that irregular heavy drinking occasions are associated with a higher risk of IHD compared with regular moderate drinking in the same range of average weekly alcohol intake. It seems that any cardioprotective effect of moderate alcohol consumption is negated by irregular heavy drinking occasions. In turn, the cardioprotective effect of regular, moderate alcohol consumption discussed in the many studies reporting average alcohol intake without taking into account irregular heavy drinking occasions might have been underestimated. The magnitude of the underestimation depends on the prevalence of irregular heavy drinking occasions in the respective population.

Nevertheless, many questions about the cardioprotective effect of alcohol consumption remain unanswered. In particular, assessment of exposure to alcohol was very different across studies, and we look forward to new studies investigating heavy drinking occasions more accurately. We encourage other researchers to take into account, where possible, the modifying effect of irregular heavy drinking episodes in future reports.

What consequences do our findings have? Depending on the proportion of episodic heavy drinkers in a population, the attributable fraction of alcohol consumption for IHD could be substantially different from what has been

estimated in the past without taking into account a separate risk function for heavy episodic drinking patterns. Heavy drinking episodes pose a serious threat to public health, not only in terms of violence and drunk driving but also in terms of IHD incidence. Because of high prevalence of alcohol consumption as a risk factor and IHD as a cause of death worldwide, the results of this study are of great public health relevance. Population surveys estimate that the proportion of such drinking behavior is 20%–25% in North America (88, 89), with the majority of light to moderate drinkers reporting at least occasional heavy drinking episodes (90). Heavy drinking occasions are also common in Europe (6). Therefore, recommendations and guidelines on alcohol consumption for the general public should be carefully examined and tailored to the population at risk. Low-risk drinking guidelines should be carefully reevaluated based on the findings from this study to incorporate evidence for the difference in IHD risk due to irregular heavy drinking occasions (91), not only for primary prevention of harmful effects due to alcohol consumption but also for considering requests for alcohol consumption as a secondary prevention measure that occur from time to time in the literature.

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