Ischemic Heart Disease Mortality and Morbidity Rates in Former Drinkers: A Meta-Analysis

Michael Roerecke* and Jürgen Rehm

* Correspondence to Michael Roerecke, Social and Epidemiological Research, Centre for Addiction and Mental Health, 33 Russell Street, Room T425, Toronto, Ontario, Canada M5S 2S1 (e-mail: m.roerecke@web.de).

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Current abstainers from alcohol have been identified as an inadequate reference group in epidemiologic studies of the effects of alcohol, because inclusion of former drinkers might lead to overestimation of the protective effects and underestimation of the detrimental effects of drinking alcohol. The authors’ objective in the current study was to quantify this association for ischemic heart disease (IHD). Electronic databases were systematically searched for relevant case-control or cohort studies published from 1980 to 2010. Thirty-eight articles fulfilled the inclusion criteria, contributing a total of 5,613 IHD events and 12,097 controls among case-control studies and 1,387 events with combined endpoints and 7,183 events stratified by endpoint among 232,621 persons at risk among cohort studies. Pooled estimates for the subset stratified by sex and endpoint showed a significantly increased risk among former drinkers compared with long-term abstainers for IHD mortality (among men; relative risk = 1.25, 95% confidence interval: 1.15, 1.36; among women relative risk = 1.54, 95% confidence interval: 1.17, 2.03). For IHD morbidity, the estimates for both sexes were close to unity and not statistically significant. Results were robust in several sensitivity analyses. In future studies, researchers should separate former drinkers from the reference category to obtain unbiased effect estimates. Implications for the overall beneficial and detrimental effects of alcohol consumption on IHD are discussed below.

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

Abbreviations: CI, confidence interval; ICD, International Classification of Diseases; IHD, ischemic heart disease.
recent epidemiologic studies showed a more pronounced
effect of alcohol on mortality rates than on morbidity rates
(10, 11).

MATERIALS AND METHODS

Search strategy

We systematically searched for potentially relevant origi-
nal articles written from January 1980 to the second week
of April 2010 in the following electronic databases: MED-
LINE, EMBASE, Web of Science (Science Citation Index
Expanded, Social Sciences Citation Index, Arts and Human-
ities Citation Index), ETOH (Alcohol and Alcohol Problems
Science Database, National Institute on Alcohol Abuse and
Alcoholism (January 1980–December 2003)), and AIM (Al-
cohol in Moderation, alcohol industry database). Reference
lists of identified papers, relevant reviews (12–20), and
meta-analyses (1, 21–26) were scrutinized for additional
articles. Because of resource limitations, we did not search
the gray literature. Excluding letters, editorials, conference
abstracts, reviews, and comments, we used the following
free-text keywords and subject headings to identify relevant
articles: (alcohol drinking OR alcoholic beverages OR bev-
erages OR (alcohol AND (drinking or intake or consump-
tion) OR (ethanol AND drinking or intake or consump-
tion))) AND (myocardial ischemia OR myocardial infarct* OR
corony disease OR heart diseases OR coronary artery dis-
ease OR coronary heart disease OR angina OR cardiac
death* OR ischaemic heart disease OR ischemic heart dis-
ease OR cardiac event* OR coronary event*) AND (cohort
studies OR epidemiologic studies OR follow-up studies OR
longitudinal studies OR prospective studies OR case-control
studies OR retrospective studies) AND (ratio* OR risk*).
No language restrictions were applied. Inclusion criteria
were: 1) being a case-control or cohort study; 2) reporting
IHD as a separate outcome (International Classification of
Diseases (ICD), Ninth Revision, codes 410–414 and ICD,
Tenth Revision, codes I20–I25); 3) using an exposure mea-
surement that referred to overall alcohol consumption and
not only to selected beverages; 4) reporting a measure of
risk and its corresponding measure of variability for former
drinkers compared with abstainers (or sufficient data to cal-
culate those risks); and 5) containing estimates that were at
least age-adjusted. Exclusion criteria were: 1) self-reporting
of IHD morbidity or cardiovascular outcomes combined
(i.e., including stroke); 2) being a cross-sectional study;
3) not reporting effect estimates for former drinking; and
4) containing estimates that were not age-adjusted. One
author performed the search and excluded studies at the first
exclusion pass based on title and abstract. Studies identified
for a more detailed assessment (any reported measure of
alcohol consumption and IHD as an outcome) were dis-
cussed and agreed upon by both authors.

Definition of former drinkers

Measurement error is a common issue in alcohol re-
search. Many different definitions for former drinker have
been used in primary studies. Generally, those definitions
could be divided into 2 groups. First were studies that clas-
sified drinking groups by asking the respondents if they
were never, past, or current drinkers (27–30). This type of
assessment separates abstainers from former drinkers in
a qualitative form. Then there were studies that asked about
abstention with an upper quantitative limit, sometimes fre-
quency of drinking days per time period only or frequency
of drinks per time period. Examples for those definitions
included never or less than once a month (31), or the ques-
tion, “Did you ever drink 12 or more drinks in your life-
time?” (9, 32, 33).

A recent discussion examined the most suitable reference
group for and adequate operationalization of lifetime ab-
stention (22, 34, 35). For example, should somebody who
answered “never or almost never” to the question, “Did you
drink alcohol in the past?” be classified as a lifetime ab-
stainer? In most studies, this would be considered lifetime
abstention, even if researchers could not exclude the possi-
bility that the person did consume some alcohol in the past.
As no specific limit was given for the amount of alcohol
consumed, we classified such an assessment as qualitative
rather than quantitative. Given these operationalizations, our
reference group for assessing the effects of former drinking
should be labeled as “long-term abstainers or very light
drinkers.” Because of the various operationalizations used
in the selected studies, we tested potential changes in pooled
relative risk estimates caused by different approaches to
measurement of abstention in our analyses.

Data extraction

Hazard ratios, relative risks, and odds ratios were treated
as equivalent measures of relative risk. In case the reference
category included not only long-term abstainers but also, for
example, moderate drinkers, we recalculated the effect size
measure to reflect abstainers as the reference category. In
cases where no confidence interval, standard error, or var-
iance for a risk estimate was reported, we estimated the cor-
sponding standard error from the raw numbers of cases
and controls (or persons at risk) (36, 37). We abstracted
information on age, number of cases and controls or persons
at risk, study design, endpoint, country, and adjustment for
confounder. We used maximally adjusted risk estimates (ad-
justed at least for age) where possible; however, we avoided
estimates adjusted for blood pressure because blood pres-
sure represented a mediator on the causal pathway between
alcohol consumption and IHD rather than a confounder
(38–41), which could result in underestimation of the true
relation (42). When estimates stratified by endpoint (mor-
tality and morbidity) were available, sex, and race, we chose
those and prepoled the estimates in cases in which >1
estimate was reported within those categories (43).

Statistical analysis

Within each sex and endpoint stratum, we pooled esti-
mates to derive 1 set per article by using fixed-effects esti-
mates weighted by the inverse of their variance. When only
estimates using combined endpoints or sex were reported,
those estimates were included in all respective strata. All
analyses concerning risk were performed on the natural log scale. To account for possible significant between-study heterogeneity, we used DerSimonian-Laird random-effect models (44) to derive a pooled effect across studies in which the between-study variance was estimated in addition to the specified within-variance component. We quantified inconsistencies across studies and their impact on the analysis by using Cochrane’s $Q$ (45) and the $I^2$ statistic (46). $I^2$ can be interpreted as the proportion of the total variation in the estimated slopes for each study that is due to heterogeneity between studies. Possible publication bias was explored by using funnel plots of the (log-transformed) effect sizes against their standard error and a formal regression-based test by Peters et al. (47). We tested adjustment for age only as well as adjustment for social class or educational level in separate meta-regression models to investigate their influence on the pooled effect size.

We performed several sensitivity analyses using the following methods of inclusion or exclusion: 1) excluding studies that reported estimates for combined sex and endpoint; 2) excluding studies that reported estimates for combined sex and endpoint or combined endpoint, but stratified by sex; 3) excluding studies that reported estimates for combined sex and endpoint or combined sex, but stratified by endpoint; 4) excluding all studies that were not sex- and endpoint-specific; 5) excluding studies that used current abstinence at 2 time points or assessed alcohol intake for $\leq 20$ years; 6) including only studies that used a qualitative measure of long-term alcohol intake (including all studies that did not specify an upper quantitative limit for lifetime alcohol intake); and 7) including only studies that defined abstinence as $< 1$ drinking occasion per month or $< 1$ drink per month during a person’s lifetime. Sensitivity analyses 1–4 investigated the accuracy of endpoint classification and sex, whereas sensitivity analyses 5–7 investigated the definition of abstention used in the respective studies. All analyses were conducted using Stata statistical software, version 10.1 (48).

RESULTS

The search revealed 1,538 unique citations (Figure 1). Of those, 1,146 were excluded on the first exclusion pass based on the title and abstract. We retrieved 392 full papers and scanned them to determine whether the authors should be included. Of those, 113 were excluded because the authors...
Table 1. Characteristics of 38 Articles Selected for Quantitative Analysis of the Effect of Former Drinking on Ischemic Heart Disease Risk, 1980–2010

<table>
<thead>
<tr>
<th>Study</th>
<th>Sex</th>
<th>Study Design</th>
<th>Endpoint</th>
<th>No. of Cases</th>
<th>Total Sample Size*</th>
<th>Country</th>
<th>Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenberg et al., 1981 (51)</td>
<td>Female</td>
<td>Case-control</td>
<td>Morbidity</td>
<td>149</td>
<td>337</td>
<td>United States</td>
<td>Age, hospital, religion, educational level, menopausal status, physician contacts, smoking, hypertension, diabetes, abnormal blood lipids, obesity, year of admission, and contraceptive use</td>
</tr>
<tr>
<td>Kaufman et al., 1985 (59)</td>
<td>Male</td>
<td>Case-control</td>
<td>Morbidity</td>
<td>220</td>
<td>339</td>
<td>United States</td>
<td>Age and smoking</td>
</tr>
<tr>
<td>Kono et al., 1986 (49)</td>
<td>Male</td>
<td>Cohort</td>
<td>Mortality</td>
<td>86</td>
<td>1,570</td>
<td>Japan</td>
<td>Age and smoking</td>
</tr>
<tr>
<td>Klatsky et al., 1986 (61)</td>
<td>Both (combined)</td>
<td>Cohort</td>
<td>Morbidity</td>
<td>184</td>
<td>11,076</td>
<td>United States</td>
<td>Age, sex, race, smoking, coffee intake, and educational level</td>
</tr>
<tr>
<td>Lazarus et al., 1991 (62)</td>
<td>Both (separate)</td>
<td>Cohort</td>
<td>Mortality</td>
<td>64</td>
<td>903</td>
<td>United States</td>
<td>Age</td>
</tr>
<tr>
<td>Jackson et al., 1991 (31)</td>
<td>Both (separate)</td>
<td>Case-control</td>
<td>Mortality</td>
<td>153</td>
<td>455</td>
<td>New Zealand</td>
<td>Age, smoking, hypertension, social class, exercise level, and recent change in drinking</td>
</tr>
<tr>
<td>Kono et al., 1991 (72)</td>
<td>Both (combined)</td>
<td>Case-control</td>
<td>Morbidity</td>
<td>32</td>
<td>111</td>
<td>Japan</td>
<td>Age</td>
</tr>
<tr>
<td>Cullen et al., 1993 (53)</td>
<td>Both (separate)</td>
<td>Cohort</td>
<td>Mortality</td>
<td>124</td>
<td>739</td>
<td>Australia</td>
<td>Age, occupation, smoking, blood pressure, probable or suspected coronary heart disease, forced expiratory volume, diabetes, cholesterol, uric acid, and treatment for blood pressure</td>
</tr>
<tr>
<td>Iso et al., 1995 (57)</td>
<td>Male</td>
<td>Cohort</td>
<td>Mortality</td>
<td>11</td>
<td>744</td>
<td>Japan</td>
<td>Age</td>
</tr>
<tr>
<td>Wannamethee et al., 1997 (68)</td>
<td>Male</td>
<td>Cohort</td>
<td>Mortality</td>
<td>63</td>
<td>583</td>
<td>United Kingdom</td>
<td>Age, social class, physical activity, BMI, diabetes, angina, smoking, and medication</td>
</tr>
<tr>
<td>Rehm et al., 1997 (9)</td>
<td>Both (separate)</td>
<td>Cohort</td>
<td>Mortality</td>
<td>805</td>
<td>4,244</td>
<td>United States</td>
<td>Age and smoking</td>
</tr>
<tr>
<td>McElduff and Dobson, 1997 (64)</td>
<td>Both (separate)</td>
<td>Case-control</td>
<td>Mortality</td>
<td>973</td>
<td>1,447</td>
<td>Australia</td>
<td>Age, smoking, blood pressure, cholesterol, angina, stroke, previous myocardial infarction, and diabetes</td>
</tr>
<tr>
<td>Kitamura et al., 1998 (60)</td>
<td>Male</td>
<td>Cohort</td>
<td>Mortality</td>
<td>20</td>
<td>1,493</td>
<td>Japan</td>
<td>Age, serum total cholesterol, smoking, BMI, left ventricular hypertrophy, and diabetes</td>
</tr>
<tr>
<td>Liao et al., 2000 (32)</td>
<td>Both (separate)</td>
<td>Cohort</td>
<td>Mortality</td>
<td>749</td>
<td>17,133</td>
<td>United States</td>
<td>Age</td>
</tr>
<tr>
<td>Miyake et al., 2000 (50)</td>
<td>Both (combined)</td>
<td>Case-control</td>
<td>Morbidity</td>
<td>247</td>
<td>545</td>
<td>Japan</td>
<td>Age and sex</td>
</tr>
<tr>
<td>Study</td>
<td>Type</td>
<td>Design</td>
<td>Mortality and morbidity (combined)</td>
<td>Cases</td>
<td>Controls</td>
<td>Country</td>
<td>Variables</td>
</tr>
<tr>
<td>-------------------------------</td>
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<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Spos et al., 2002 (33)</td>
<td>Both</td>
<td>Cohort</td>
<td>Mortality</td>
<td>126</td>
<td>493</td>
<td>United States</td>
<td>Age, social class, smoking, BMI, physical activity level, employment, prior stroke, diabetes, medication, and self-reported health status</td>
</tr>
<tr>
<td>Wannamethee and Shaper, 2002 (69)</td>
<td>Male</td>
<td>Cohort</td>
<td>Mortality</td>
<td>69</td>
<td>591</td>
<td>United Kingdom</td>
<td>Age, sex, smoking, BMI, physical activity level, employment, prior stroke, diabetes, medication, and self-reported health status</td>
</tr>
<tr>
<td>Romelsjö et al., 2003 (66)</td>
<td>Both</td>
<td>Case-control</td>
<td>Morbidity</td>
<td>141</td>
<td>294</td>
<td>Sweden</td>
<td>Age, hospital, marital status, socioeconomic status, smoking, physical activity, cardioatherosclerotic disease, job strain, social anchorage, and life control</td>
</tr>
<tr>
<td>Klatsky et al., 2003 (8)</td>
<td>Both</td>
<td>Cohort</td>
<td>Mortality</td>
<td>606</td>
<td>19,692</td>
<td>United States</td>
<td>Age, race, BMI, education, marital status, smoking, and ischemic heart disease risk index</td>
</tr>
<tr>
<td>Fuchs et al., 2004 (55)</td>
<td>Male</td>
<td>Cohort</td>
<td>Mortality and morbidity (combined)</td>
<td>174</td>
<td>2,168</td>
<td>United States</td>
<td>Age, smoking (cigarette-years), BMI, low density lipoprotein level, WHR, educational level, income, sport index, and diabetes</td>
</tr>
<tr>
<td>Wells et al., 2004 (70)</td>
<td>Both</td>
<td>Case-control</td>
<td>Mortality and morbidity (combined)</td>
<td>307</td>
<td>606</td>
<td>New Zealand</td>
<td>Age, smoking, saturated fat, dietary fiber, and physical activity</td>
</tr>
<tr>
<td>Trevisan et al., 2004 (67)</td>
<td>Male</td>
<td>Case-control</td>
<td>Morbidity</td>
<td>146</td>
<td>354</td>
<td>United States</td>
<td>Age, education, smoking, saturated fat, dietary fiber, and physical activity</td>
</tr>
<tr>
<td>Grønbæk et al., 2004 (74)</td>
<td>Both</td>
<td>Cohort</td>
<td>Mortality</td>
<td>228</td>
<td>4,104</td>
<td>Denmark</td>
<td>Age, sex, smoking, educational level, and BMI</td>
</tr>
<tr>
<td>Negri et al., 2005 (75)</td>
<td>Both</td>
<td>Case-control</td>
<td>Morbidity</td>
<td>150</td>
<td>278</td>
<td>Italy</td>
<td>Age and sex</td>
</tr>
<tr>
<td>Mäkelä et al., 2005 (71)</td>
<td>Male</td>
<td>Cohort</td>
<td>Mortality and morbidity (combined)</td>
<td>94</td>
<td>413</td>
<td>Finland</td>
<td>Age, cohort period, marital status, educational level, and smoking</td>
</tr>
<tr>
<td>Kabagambe et al., 2005 (58)</td>
<td>Both</td>
<td>Case-control</td>
<td>Morbidity</td>
<td>1,070</td>
<td>2,055</td>
<td>Costa Rica</td>
<td>Age and smoking</td>
</tr>
<tr>
<td>Doll et al., 2005 (73)</td>
<td>Male</td>
<td>Cohort</td>
<td>Mortality</td>
<td>149</td>
<td>989</td>
<td>United Kingdom</td>
<td>Age, sex, smoking, educational level, and BMI</td>
</tr>
<tr>
<td>Mukamal et al., 2006 (65)</td>
<td>Both</td>
<td>Cohort</td>
<td>Mortality and morbidity (combined)</td>
<td>402</td>
<td>2,162</td>
<td>United States</td>
<td>Age, race, smoking, educational level, marital status, smoking, exercise, depression, aspirin use, BMI, and diabetes</td>
</tr>
<tr>
<td>Maraldi et al., 2006 (63)</td>
<td>Both</td>
<td>Cohort</td>
<td>Mortality and morbidity (combined)</td>
<td>216</td>
<td>1,756</td>
<td>United States</td>
<td>Age, sex, and race</td>
</tr>
<tr>
<td>Harriss et al., 2007 (56)</td>
<td>Both</td>
<td>Cohort</td>
<td>Mortality</td>
<td>92</td>
<td>12,262</td>
<td>Australia</td>
<td>Age, country of birth, smoking, and daily energy and fruit intake</td>
</tr>
</tbody>
</table>

Table continues
<table>
<thead>
<tr>
<th>Study</th>
<th>Sex</th>
<th>Study Design</th>
<th>Endpoint</th>
<th>No. of Cases</th>
<th>Total Sample Size&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Country</th>
<th>Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dorn et al., 2007 (54)</td>
<td>Female</td>
<td>Case-control</td>
<td>Morbidity</td>
<td>202</td>
<td>938</td>
<td>United States</td>
<td>Age, BMI, educational level, race, smoking, and menopausal status</td>
</tr>
<tr>
<td>Burke et al., 2007 (52)</td>
<td>Both (combined)</td>
<td>Cohort</td>
<td>Mortality and morbidity (combined)</td>
<td>130</td>
<td>249</td>
<td>Australia</td>
<td>Age, sex, and accessibility to alcohol</td>
</tr>
<tr>
<td>Ikehara et al., 2008 (29)</td>
<td>Both (separate)</td>
<td>Cohort</td>
<td>Mortality</td>
<td>445</td>
<td>51,909</td>
<td>Japan</td>
<td>Age</td>
</tr>
<tr>
<td>Schooling et al., 2008 (28)</td>
<td>Both (separate)</td>
<td>Cohort</td>
<td>Mortality</td>
<td>344</td>
<td>45,227</td>
<td>China</td>
<td>Age, smoking, education, housing, monthly expenditure, BMI, and physical activity level</td>
</tr>
<tr>
<td>Schooling et al., 2009 (30)</td>
<td>Both (separate)</td>
<td>Case-control</td>
<td>Mortality</td>
<td>1,823</td>
<td>9,951</td>
<td>China</td>
<td>Age, sex, education, physical activity level, occupational physical activity level, and smoking</td>
</tr>
<tr>
<td>Ikehara et al., 2009 (27)</td>
<td>Male</td>
<td>Cohort</td>
<td>Mortality</td>
<td>104</td>
<td>4,888</td>
<td>Japan</td>
<td>Age</td>
</tr>
<tr>
<td>Mukamal et al., 2010 (76)</td>
<td>Both (combined)</td>
<td>Cohort</td>
<td>Mortality</td>
<td>3,134</td>
<td>65,563</td>
<td>United States</td>
<td>Age, sex, race, smoking, marital status, educational level, region, urbanization, BMI, and general health status</td>
</tr>
<tr>
<td>Arriola et al., 2010 (77)</td>
<td>Both (separate)</td>
<td>Cohort</td>
<td>Mortality and morbidity (combined)</td>
<td>151</td>
<td>12,584</td>
<td>Spain</td>
<td>Age, center, smoking, height, educational level, physical activity level, WHR, vitamin E intake, antithrombotic and antihemorrhagic drug use, and energy intake</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; WHR, waist-to-hip ratio.

<sup>a</sup> Current abstainers.
did not report any estimates for alcohol consumption or enough data to allow us to calculate those estimates, 45 were excluded because IHD was not reported as an outcome, and 15 were excluded because of the study design. Out of the remaining 219 articles, authors in 175 did not assess or report an estimate for former drinkers (26 of these were duplicate reports from studies that were selected), leaving 44 original articles for inclusion. After removing duplicate reports (n = 6) of studies already included in the meta-analysis, 38 unique articles remained for a quantitative analysis (8, 9, 27–33, 49–77). Overall, we considered our analysis a good selection of alcohol-related studies, in particular considering that the studies excluded simply did not assess former drinking and were of lesser quality with respect to alcohol exposure in general, particularly abstention.

Among the articles selected for a quantitative analysis, 3 reported only 1 estimate for sex and endpoint combined, 8 reported estimates for mortality and morbidity combined, and 7 reported estimates for both sexes by endpoint (Table 1). These estimates were used in any of the respective analyses labeled as all available estimates, whereas the 20 articles reporting sex- and endpoint-specific estimates were used in the analyses labeled as estimates stratified by sex and endpoint.

A total of 5,613 IHD events with 12,097 controls among case-control studies and 1,387 events with combined endpoints and 7,183 events stratified by endpoint among 232,621 persons at risk among cohort studies (taking into account multiple articles per study) were used in this analysis. Selected articles originated in the United States (n = 14), Japan (n = 7), Australia (n = 4), the United Kingdom (n = 3), New Zealand (n = 2), and China (n = 2), with an additional 1 study each from Denmark, Sweden, Spain, Finland, Italy, and Costa Rica (Table 1). Only 3 articles based on 2 studies (9, 33, 55) provided estimates stratified by race. We therefore refrained from analyzing those separately and included each estimate in the respective sex and endpoint strata.

The proportion of former drinkers among current abstainers varied considerably across the primary studies and strata examined. The mean percentages of former drinkers among current abstainers were between 16% and 90% among men and between 1% and 74% among women. Although the percentage of former drinkers covered a wide range across studies, the percentage was not associated with the effect size regardless of whether all estimates or estimates stratified by sex and endpoint were considered in any of the strata in our analyses, as all correlation coefficients were small in magnitude and not significant (Table 2).

Taking into account only studies that reported primary estimates stratified by sex and endpoint, the pooled random-effect relative risk estimate for IHD mortality among men (Figure 2) was 1.25 (95% confidence interval (CI): 1.15, 1.36), with little heterogeneity (I² = 26.4%; χ² (13 df) = 17.67, P = 0.17) (Table 3). Among women (Figure 3), the summary random-effects relative risk estimate for mortality was 1.54 (95% CI: 1.17, 2.03), with substantial heterogeneity (I² = 71.1%; χ² (9 df) = 31.12, P < 0.001). The effect for

### Table 2. Proportion of Former Drinkers Among Current Abstainers, by Sex and Endpoint, 1980–2010

<table>
<thead>
<tr>
<th>Sex, Endpoint, and Model</th>
<th>No. of Studies</th>
<th>% of Former Drinkers</th>
<th>r^b</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Weighted Mean</td>
<td>Minimum</td>
<td>Maximum</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality All available estimates (combined sex or endpoint included)</td>
<td>27</td>
<td>31</td>
<td>16</td>
<td>83</td>
</tr>
<tr>
<td>Stratified by sex and endpoint</td>
<td>14</td>
<td>32</td>
<td>16</td>
<td>70</td>
</tr>
<tr>
<td>Morbidity All available estimates (combined sex or endpoint included)</td>
<td>23</td>
<td>37</td>
<td>16</td>
<td>90</td>
</tr>
<tr>
<td>Stratified by sex and endpoint</td>
<td>5</td>
<td>61</td>
<td>31</td>
<td>90</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality All available estimates (combined sex or endpoint included)</td>
<td>18</td>
<td>16</td>
<td>1</td>
<td>47</td>
</tr>
<tr>
<td>Stratified by sex and endpoint</td>
<td>10</td>
<td>8</td>
<td>2</td>
<td>33</td>
</tr>
<tr>
<td>Morbidity All available estimates (combined sex or endpoint included)</td>
<td>17</td>
<td>25</td>
<td>1</td>
<td>74</td>
</tr>
<tr>
<td>Stratified by sex and endpoint</td>
<td>5</td>
<td>38</td>
<td>14</td>
<td>74</td>
</tr>
</tbody>
</table>

^a^ Among all current abstainers.

^b^ Pearson’s correlation coefficient of proportion of former drinkers with effect size.
IHD morbidity (Figures 4 and 5) as an endpoint was slightly >1 among women (relative risk = 1.05, 95% CI: 0.69, 1.60), and <1 for men (relative risk = 0.85, 95% CI: 0.70, 1.04). Neither estimate, however, was statistically significant. Significantly elevated relative risks for IHD-related death but not for IHD-related morbidity remained in the analysis after estimates for combined sex or endpoint were included (Table 3). Adjustment for neither age only (where applicable) nor social class was statistically significantly related to the pooled effect estimate for male mortality ($P = 0.16$ and $P = 0.73$, respectively), male morbidity (social class: $P = 0.99$), female mortality ($P = 0.97$ and $P = 0.78$), and female morbidity (social class: $P = 0.75$). Results were similar when estimates for combined sex or endpoint were included.

We did not find any evidence of publication bias among men ($P = 0.44$ and $P = 0.49$ for mortality and morbidity, respectively) or women ($P = 0.70$ and $P = 0.42$ for mortality and morbidity, respectively). Omitting each study one by one and reestimating the models did not reveal any substantial divergence from the overall pooled estimates. Although all of these studies showed a reasonable distinction between long-term abstainers and former drinkers, we also conducted several sensitivity analyses with regard to stratification of reported estimates by endpoint and sex and to definition of abstention. These sensitivity analyses did not reveal any substantial differences in pooled effect estimates.

Three studies stood out in their measurements of alcohol exposure. Two reported on current nondrinking at 2 points in time (62, 74), and 1 (49) assessed nondrinking status (and all other drinking categories) for the past 20 years at baseline. Excluding those 3 studies resulted in only marginally different pooled estimates among male and female mortality rates, for which those studies reported estimates.

**DISCUSSION**

Correct identification of drinking groups is crucial for determining the dose–response relation between alcohol consumption and IHD risk. In this article, we summarized current epidemiologic evidence for a risk difference between former drinkers and long-term abstainers. Our results showed that there was a substantial difference in IHD risk depending on whether the endpoint was mortality or morbidity. Former drinkers were at an increased risk for IHD when mortality was considered as an endpoint for both sexes, and pooled estimates were statistically significant with similar effect sizes. However, we did not find evidence for an effect of former drinking on morbidity rates in our analysis. In other words, in our meta-analysis, we found evidence for the “sick quitter effect” as an outcome measurement for mortality but not for morbidity. The reasons behind this difference by endpoint are unclear. Aside from assuming a real biologic effect of former drinking,
methodological properties, such as differences in outcome ascertainment or study design in general, could also explain this effect. When comparing pooled relative risks for IHD-related mortality and morbidity using only primary estimates that were stratified by sex and endpoint, it is important to consider that this effectively represents a comparison of study design, because all but 1 estimate for mortality were from cohort studies, and all but 2 estimates for morbidity were from case-control studies. However, there were fewer studies available for a stratified analysis of morbidity as an endpoint, thus limiting the conclusions about this relation. Although we cannot rule out residual confounding as an explanation for our results, meta-regression models did not reveal a significant influence of differential adjustment across studies. Nevertheless, this issue deserves further study, and we encourage researchers to report more detailed results of any type of regression modeling to allow better judgment of the effect of adjusting for potential confounders of the alcohol–heart disease relation.

Several other limitations apply as well. Although the cardioprotective association of regular, low-to-moderate alcohol consumption is well-established (1), with convincing experimental evidence regarding plausible biologic pathways (78), alcohol consumption in relation to IHD risk is more complex in both biologic mechanisms and drinking behavior over the lifetime than we were able to investigate with the current data. For example, we were unable to examine former drinking behavior (length and variability of past alcohol exposure) in detail because of the lack of data. Compared with long-term abstainers, former drinkers could show a lower IHD risk when former drinking was mostly regular moderate drinking and an increased risk when former drinking was mostly characterized by irregular heavy drinking or regular heavy drinking. There is some evidence that the proportion of occasional (infrequent) drinkers among current abstainers can be much higher than that of true lifetime abstainers (79). Again, it will depend on the operationalization of the word occasional. To give an example, it is inconceivable that drinking alcohol on 20 occasions during one’s lifetime could have a biologic effect on IHD (34, 35). On the other hand, occasional drinking once a month, and often in binges, may have an effect on IHD (80). Reports have shown that it is almost impossible to differentiate between lifetime abstainers and very infrequent drinkers in retrospective studies, as large fractions of self-identified lifetime abstainers report at least some drinking (35, 79). This implies that repeated measures of exposure would be good epidemiologic practice in studies on alcohol as a risk factor. In addition, the proportion of current abstainers in a population typically varies across and within countries, more so among women than among men (81, 82). Although the proportion may vary, the relative risk should not be biased (83). One might also argue that the large variability of the proportion of former drinkers among current abstainers warrants cautious interpretation and limits the generalizability of the results of our study; however, we found no evidence of such an effect.

| Table 3. Pooled Relative Risks for Ischemic Heart Disease\(^a\) in Former Drinkers Compared With Long-Term Abstainers, by Sex and Endpoint, 1980–2010 |
|-----------------|-----------------|-----------------|-----------------|
| **Sex, Endpoint, and Model** | **No. of Studies** | **Pooled Relative Risk** | **95% Confidence Interval** | \(I^2, \%\) |
| **Men** | | | | |
| Mortality | | | | |
| All available estimates (combined sex or endpoint included) | 27 | 1.21\(^b\) | 1.11, 1.33 | 33.3 |
| Stratified by sex and endpoint | 14 | 1.25 | 1.15, 1.36 | 26.4 |
| Morbidity | | | | |
| All available estimates (combined sex or endpoint included) | 23 | 0.97 | 0.89, 1.06 | 5.2 |
| Stratified by sex and endpoint | 5 | 0.85 | 0.70, 1.04 | 10.6 |
| **Women** | | | | |
| Mortality | | | | |
| All available estimates (combined sex or endpoint included) | 18 | 1.36\(^b\) | 1.16, 1.60 | 63.3 |
| Stratified by sex and endpoint | 10 | 1.54\(^b\) | 1.17, 2.03 | 71.1 |
| Morbidity | | | | |
| All available estimates (combined sex or endpoint included) | 17 | 1.08\(^b\) | 0.93, 1.24 | 42.0 |
| Stratified by sex and endpoint | 5 | 1.05\(^b\) | 0.69, 1.60 | 64.9 |

\(a\) Includes International Classification of Diseases, Ninth Revision, codes 410–414 and International Classification of Diseases, Tenth Revision, codes I20–I25.

\(^b\) Random-effects models.
When considering measurement of IHD incidence and IHD death, differences in classification of the outcome across countries and studies might explain our results from a methodological point of view. Recent studies have shown that a further stratification within the ICD codes for IHD might be necessary, because these studies have shown differences in coding of the underlying cause of death across countries (84–86). In addition, the exposure-outcome relation may contain more complexities than has been appreciated thus far. In a Russian study, Zaridze et al. (87) reported that acute IHD other than myocardial infarction (ICD-10 code I24, the most common cause of heart disease in that study) showed a particularly strong detrimental relation to average alcohol intake without any cardioprotective associations. Nevertheless, their study also found that a substantial fraction of subjects who were originally classified as having IHD in fact had alcohol poisoning, although the typically detrimental pattern of irregular heavy drinking occasions in Russia also needs to be considered in this case. However, little data exist to confirm this phenomenon in other countries and different drinking cultures.

Although the sick quitter effect assumes that former drinkers stopped drinking for health reasons, we could not be sure that this was the case in the studies included in this analysis. A recent methodological study in the United States found that slightly more than half of former drinkers who lost control of their drinking also reported serious health effects because of their drinking (88). Regardless of the reason why they stopped drinking, a former drinker’s increased risk of death is unlikely to explain away the cardioprotective association commonly found for moderate regular drinking. Adjusting a relative risk of 0.80 (the nadir of the J-shaped dose-response curve described by Corrao et al. (1)) among men with our pooled relative risk using only estimates stratified by sex and endpoint for former drinking (relative risk = 1.25, assuming 32% of current abstainers were former drinkers) showed that the corrected relative risk was 0.86 when the effect of former drinking was taken into account. In other words, the cardioprotective association of alcohol might be slightly overestimated when the wrong comparison group is selected, but this factor cannot be used as an argument to doubt the cardioprotective association per se.

Our results underline the importance of correct identification of the reference group if the J-curve commonly found in epidemiologic studies on alcohol consumption and IHD risk is to be further refined. This has ultimately important implications for the choice of the reference group in any epidemiologic study on alcohol consumption in relation to IHD. However, explanations for this difference are speculative thus far. The difference in risk among former drinkers seems to be dependent on either the type of outcome measure, namely mortality and morbidity, or the study design (cohort studies showed a significant effect, whereas case-control studies did not). Although it was beyond the scope of this analysis to determine potential reasons

Table: Relative Risk of Ischemic Heart Disease Mortality among Former Drinkers Compared with Abstainers in Women, Stratified by Sex and Endpoint

<table>
<thead>
<tr>
<th>Author, Year (Reference No.)</th>
<th>Relative Risk (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lazarus et al., 1991 (62)</td>
<td>3.53 (1.92, 6.46)</td>
<td>9.72</td>
</tr>
<tr>
<td>Jackson et al., 1991 (31)</td>
<td>1.10 (0.20, 4.20)</td>
<td>2.76</td>
</tr>
<tr>
<td>Cullen et al., 1993 (53)</td>
<td>2.47 (0.76, 8.05)</td>
<td>4.18</td>
</tr>
<tr>
<td>Rehm et al., 1997 (9)</td>
<td>2.32 (1.57, 3.41)</td>
<td>13.48</td>
</tr>
<tr>
<td>Liao et al., 2000 (32)</td>
<td>1.09 (0.97, 1.22)</td>
<td>17.87</td>
</tr>
<tr>
<td>Klatsky et al., 2003 (8)</td>
<td>1.10 (0.81, 1.49)</td>
<td>15.01</td>
</tr>
<tr>
<td>Harriss et al., 2007 (56)</td>
<td>1.34 (0.53, 3.42)</td>
<td>5.90</td>
</tr>
<tr>
<td>Ikehara et al., 2008 (29)</td>
<td>1.10 (0.49, 2.47)</td>
<td>7.09</td>
</tr>
<tr>
<td>Schooling et al., 2008 (28)</td>
<td>1.30 (0.80, 2.13)</td>
<td>11.62</td>
</tr>
<tr>
<td>Schooling et al., 2009 (30)</td>
<td>1.82 (1.16, 2.84)</td>
<td>12.37</td>
</tr>
<tr>
<td>Overall</td>
<td>1.54 (1.17, 2.03)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Figure 3. Pooled relative risk of ischemic heart disease mortality among former drinkers compared with abstainers in women, stratified by sex and endpoint. Weights are from random-effects models, 1980–2010. CI, confidence interval.
for differential effects, they may also include outcome assessment, which might be more valid when disease incidence rather than death is concerned, or exposure measurement because the length and type (light, regular, irregular, or heavy regular alcohol consumption) of former drinking behavior should determine the lifetime IHD risk. All those groups might be associated with differential risk based on their former drinking pattern and the length of such a drinking pattern. To have a meaningful reference group, future studies should investigate not only the reason subjects stopped drinking but also some details about former drinking behavior.

Figure 4. Pooled relative risk of ischemic heart disease morbidity among former drinkers compared with abstainers in men, stratified by sex and endpoint, 1980–2010. CI, confidence interval.

Figure 5. Pooled relative risk of ischemic heart disease morbidity among former drinkers compared with abstainers in women, stratified by sex and endpoint. Weights are from random-effects models, 1980–2010. CI, confidence interval.
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Author affiliations: Centre for Addiction and Mental Health, Toronto, Ontario, Canada (Michael Roerecke, Jürgen Rehm); Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada (Michael Roerecke, Jürgen Rehm); Department of Psychiatry, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada (Jürgen Rehm); and Technische Universität Dresden, Dresden, Germany (Jürgen Rehm).

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REFERENCES


