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Moderate alcohol use and reduced mortality risk: Systematic error in prospective studies

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Abstract
The majority of prospective studies on alcohol use and mortality risk indicates that abstainers are at increased risk of mortality from both all causes and coronary heart disease (CHD). This meta-analysis of 54 published studies tested the extent to which a systematic misclassification error was committed by including as 'abstainers' many people who had reduced or stopped drinking, a phenomenon associated with ageing and ill health. The studies judged to be error free found no significant all-cause or cardiac protection, suggesting that the cardiac protection afforded by alcohol may have been over-estimated. Estimates of mortality from heavier drinking may also be higher than previously estimated.

Keywords: *Coronary heart disease mortality, meta-analysis, prospective studies, systematic error, cardiac protection*

Introduction

A substantial literature supports the hypothesis that alcohol use protects against the incidence of coronary heart disease (CHD). Epidemiological evidence for a

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protective effect comes in large part from prospective mortality studies of alcohol use and all-cause mortality where a ''J-shape'' curve is commonly found – abstainers from alcohol and, especially, heavier drinkers are at highest risk whereas light drinkers are at lowest risk. The J-shape curve is thought to derive from an inverse association found between alcohol use and CHD mortality risk – abstainers are at increased risk compared to drinkers. Higher all-cause risk for heavier drinkers is due to associations with other diseases whereas the risk among abstainers to the absence of the use of alcohol, making them vulnerable to CHD. These findings have been replicated in studies worldwide and reported in meta-analyses, prospective morbidity studies, and case control studies (Corrao, Rubbiati, Bagnardi, Zambon, & Poikolainen, 2000; English et al., 1995; Gmel, Gutjahr, & Rehm, 2003; Holman, English, Milne, & Winter, 1996; Maclure, 1993; Rehm, Gutjahr, & Gmel, 2001). Clinical trials and biomedical studies have confirmed plausible biological mechanisms for cardiac protection (e.g., Rimm, Williams, Fosher, Criqui, & Stampfer, 1999). This total literature has had significant influence on public health policies and clinical advice.

In 1988 Shaper, Wannamethee and Walker (1988) suggested that the higher abstainer risk was created by the *reduction* or *termination* of drinking in older people due to increased illness, disability, frailty and/or medication use. However, by 1996, alcohol's coronary advantage was considered well established (Klatsky, 1996) because abstainers were found at greater risk despite efforts in some studies to remove or separate former drinkers and/or exclude persons with pre-existing symptoms or CHD diagnosis. The possibility that including occasional drinkers in the abstainer category might also create bias was also not considered. This oversight is likely due to the view that occasional drinking would not be enough to gain the protective effect as posited by the potential biological mechanisms for this effect. The difficulty of assessing shifts in drinking behavior over time also may have caused misclassification errors. The present study sought to identify the extent to which these potential misclassification errors were present in prospective studies and whether they influenced the extent to which protective effects were found.

The evidence that alcohol consumption declines with advancing age in nearly all societies is compelling from cross-sectional studies (Cryer et al., 1999; Cryer et al., 2001; Graham & Schmidt, 1988; Knupfer & Room, 1970; Kunz, 1997; Ruchlin, 1997; Zarkin, Bray, Babor, & Higgins-Biddle, 2004), prospective mortality studies (DeLabry, Glynn, & Levenson, 1992; Goldberg, Burchfiel, Reed, Wergowske, & Chiu, 1994; Kittner et al., 1983; Klatsky, Friedman, & Siegelaub, 1981; Paunio et al., 1994; San Jose, Van DeMheen, Van Oers, & Mackenbach, 1999; Sesso et al., 2000; Shaper & Wannamethee, 2000; Suhonen, Aromaa, Reunanen, & Knekt, 1987) and other longitudinal studies (Adams, Garry, Rhyne, Hunt, & Goodwin, 1990; Cahalan, 1968; Dent et al., 1997; Dent et al., 2000; Gronbaek et al., 2004; Seppa, Pitkajarvi, & Sillanaukee, 1999; Shaper & Wannamethee, 1998; Stall, 1986). Multiple measurement longitudinal studies have found that many people shift over time between complete abstinence and occasional drinking (Fillmore et al., 1991; Kerr, Fillmore, & Bostrom, 2002;

Moore et al., 2005) and that alcohol use declines with advancing age (Rimm et al., 1991). Decline in health, in addition to changes in body chemistry and fat composition with age, is implicated in the reduction or termination of consumption and found to be disproportionate across drinking categories in both cross-sectional (Berberian, van Duijn, & Hoes, 1994; Camargo et al., 1997; Longnecker & MacMahon, 1988; San Jose et al., 1999; Serdula et al., 1995; Wannamethee & Shaper, 1997) and longitudinal studies (Eigenbrodt et al., 2001; Perreira & Sloan, 2001; Shaper & Wannamethee, 1998; Tracy, Gorman, & Leventhal, 1992; Zins et al., 1999). Statistical controls for age in these studies are insufficient to control for a strong bias toward less healthy individuals being more likely to reduce or quit drinking. Such a bias could exaggerate or create the appearance of cardiac protection in light drinkers.

Objectives

We conducted a meta-analyses of prospective mortality studies using different degrees of control for postulated sources of error. Studies were classified according to whether or not they contained either or both of the following hypothesized misclassification errors:

Former Drinker Misclassification Error: failure to separate former drinkers (no drinks in the past year) from complete abstainers;

Occasional Drinker Misclassification Error: failure to separate occasional drinkers (drinking once a month or less) from complete abstainers.

Hypotheses

(1) Studies committing *both* errors will find abstainers to be at higher risk than light drinkers (consistent with there being cardiac protection for light drinking).
(2) Studies with Former Drinker Misclassification Error but not Occasional Drinker Misclassification Error will be less likely to find this relationship.
(3) Studies with neither error and that define abstainers as long term (abstaining for more than one year) will *not* find abstainers to be at higher risk than light drinkers.
(4) Both former drinkers and occasional drinkers will be at increased mortality risk compared to abstainers and light drinkers.

Methods

Types of studies and criteria for selection

Medline and *ETOH* searches (1950s to mid 2004) were made for prospective mortality studies of the associations between alcohol use and all-cause and CHD mortality. Studies combining morbidity and mortality were eliminated. Mortality studies were evaluated because they have been the most critical for estimating population-level loss of life and have clearer and more consistent outcome

criteria. Eight studies were eliminated that combined CHD and stroke mortality risk (because opposite associations between different types of stroke and light drinking have been reported (Mazzaglia, Britton, Altmann, & Chenet, 2001)), 4 studies due to unreliable risk estimates based on 5 or fewer deaths in the reference abstainer category (Brunswick, 1984; Cahalan & Room, 1974; Temple & Leino, 1989) and one study due to no information on the definition of the drinking categories (Salonen, Puska, & Nissinen, 1983). When multiple papers were published from one study, the publication with the longest follow-up period was selected; when independent analysts published from the same dataset, one report was selected contingent on the most information for our analyses. This left a total of 54 all cause mortality studies and 35 CHD mortality studies (studies and study characteristics appended).

Some studies only partially included former drinkers in the abstainer category (Cullen, Knuiman, & Ward, 1993; Dyer et al., 1980; Klatsky, Friedman, Armstrong, & Kipp, 2003; Kono et al., 1983; Miller, Beckles, Maude, & Carson, 1990; Thun et al., 1997); these were still included as studies in the above groups containing this misclassification error but were also analyzed separately to test whether a degree of misclassification also affects the risk estimates. Additionally, the studies with neither error, where former and occasional drinkers were clearly defined, were evaluated to determine if the purposeful inclusion of these groups into the reference category altered the findings toward a protective effect.

Analysis

All analyses were conducted first on a pooled group of all studies regardless of potential misclassification of abstainers and then were categorized prior to analyses into three sub-groups depending on the types of bias in each study. Sub-groups are: Both Former and Occasional Drinker Misclassification Error, Former Drinker Misclassification Error Only, and Neither Misclassification Error. There were no studies with Occasional Drinker Misclassification Error that did not also contain Former Drinker Misclassification Error.

Drinking level in each study group was examined, first, in terms of pre-defined specific consumption levels and, second, as a continuous variable. Levels reported in each study were first converted to average grams of ethanol per day. Numbers of 'standard drinks' were converted into grams of ethanol (12 g per drink for US, 13.6 for Canadian and 10 for British, Australian and New Zealand studies). Resulting categories were then classified into pre-determined groups based on the best fit according to the range and midpoint of each group.

Drinking categories were defined as (1) former drinkers now completely abstaining, (2) occasional drinkers 1–11 drinks per year (0.033–0.363 g/day), (3) light – 1 drink/month to 2 drinks/day (0.39–24 g/day), (4) moderate – 2 to 4 drinks/day (25–44 g/day); (5) heavier – more than 4 drinks/day (National Health and Medical Research Council, 2001). All studies had an open-ended heavier drinking group, i.e., with no upper limit of quantity consumed per day for responses accepted as valid. Abstainers were categorized as: (1) long-term

abstainers if the study ascertained they had been abstinent for at least 30 days prior to interview or (2) current abstainers if the study only ascertained abstinence for 30 days or less prior to interview.

When two groups from one study fitted into one of the defined groups, both were assigned to that group. When one group from a study spanned two or more of the defined groups, the midpoint of the original group was used to determine its classification.

Mixed effect regression analyses were performed in which drinking groups and control variables were treated as fixed effects with a random study effect (Normand, 1999). The dependent variable was the log of the odds ratio, relative risk or hazard ratio for each drinking group in relation to the abstainer category. All analyses were weighted by the inverse of the estimated variance of the log odds. Variance was estimated from reported standard errors, confidence intervals or numbers of deaths.

Analyses of continuous models in SAS used mixed effects regression procedures as in the categorical models (Andreasson, 1998). The dependent variable was the log of the odds ratio, relative risk or hazard ratio for each logged alcohol volume in relation to the abstainer category and studies were weighted by the inverse of the estimated variance of the log odds. A quadratic specification of logged grams of alcohol per day was found to fit the data well and the re-transformed results presented show a clear ''J-shaped'' curve in some models.

Consideration of study characteristics

Preliminary meta-analyses determined the importance of study-level characteristics or procedures on study outcomes, evaluating the hypotheses adjusting for other study characteristics. Fifty-seven variables were considered (appended), illustrating considerable variation in study characteristics. The procedure for evaluating characteristics of studies (including whether studies adjusted for key variables) was to enter each characteristic singly in mixed effects meta-analysis regression models for its direct effect and interactions with each drinking category. Final categorical models included whether or not the study included (a) stratified for or excluded symptoms or diagnosis of CHD with or without other illnesses, (b) excluded, stratified or controlled for smoking, and measures of (c) high-density lipoprotein (HDL), (d) social class, (e) mental status and (f) disability in addition to (g) median age of the study result, (h) length of follow-up and (i) whether the study evaluated drinking in short-term recall (2 weeks or less). Some of these are regarded as more critical than others for CHD (e.g., age, gender, smoking, blood pressure, total cholesterol and prior heart disease (Normand, 1999)).

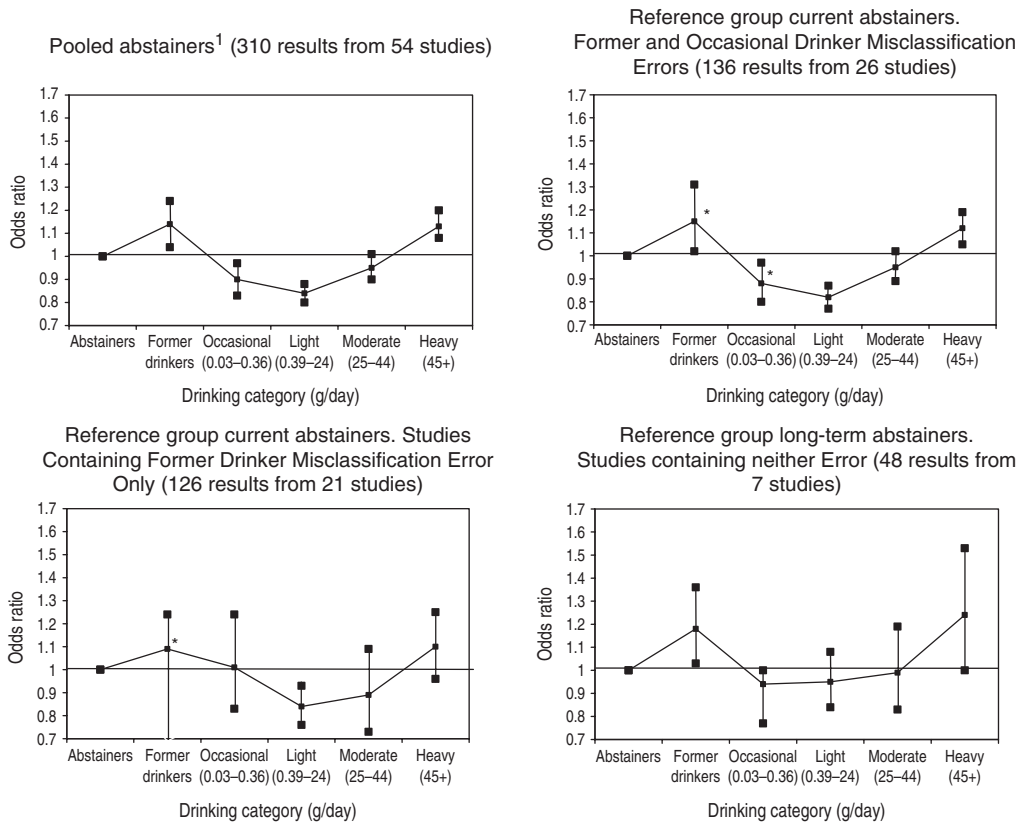
To better illustrate the heterogeneity of study results, Figure 3 shows scatter plots of study results with the re-transformed modeled curves superimposed. A single scale of grams of ethanol per day was created using either the mean (if reported) or the midpoint of reported drinking categories. Each study contained an open-ended group of the heaviest drinkers that could not be

represented by a midpoint in cases where the group mean was not reported. Therefore, a truncated log-normal distribution was fitted to the empirical drinking group distribution for each study separately. Then, the mean quantity of the resulting log-normal distribution was estimated, conditional on the quantity values lying at or above the top drinking cut-point.

Results

All cause mortality

Figure 1 shows the significant J-shaped relationship between alcohol use and all-cause mortality for the pooled group of all studies and for the group of studies with both Former and Occasional Drinker Misclassification Errors (48% of the



[1] In pooled model, former drinkers are statistically significantly higher than light drinkers.
* In some studies former drinker and/or occasional drinker misclassification errors were found but these studies classified some of their respondents as former or occasional drinkers.This accounts for the categories of former drinker or occasional drinker in these models. The number of observations for former drinkers in the studies containing both former drinker and occasional drinker misclassification is 4 and for occasional drinkers is 3. The number of observations for former drinkers in the studies containing former drinker misclassifcation error only is 2.

Figure 1. Categorical drinking group models of all-cause mortality.

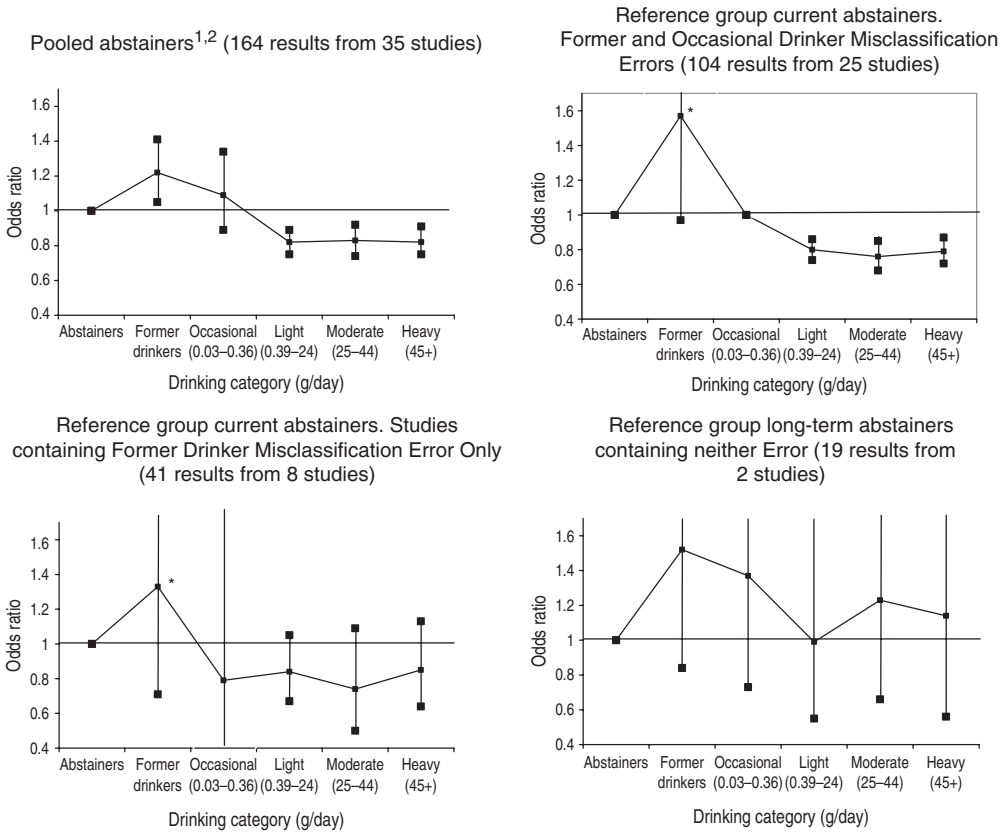
total study results). Studies with only Former Drinker Misclassification Error (39%) also showed a significant protective effect for low levels of consumption. Studies with neither misclassification error (13%) displayed no significant differences between long-term abstainers and different categories of drinkers. However the odds ratio for light drinkers and occasional drinkers is below unity and the odds ratio for heavy drinkers is elevated and close to significant indicating the possibility of significant findings with the addition of future studies. The overall shape of the curve has changed with the only significant contrast being between former drinkers and long-term abstainers. Former drinkers had an elevated mortality risk compared with both 'abstainers' and light drinkers in the pooled model.

Continuous models confirm the positive association between higher levels of drinking and mortality risk (Figure 3). Coefficients for the logged alcohol volume variables are significant at the 99% level or higher in the pooled model, while the model with neither misclassification error does not find a significant relationship overall. A J-shaped curve was fitted to each group of studies with ascent to higher risk (the point at which the odds ratio equals 1) for the pooled model and also the biased groups (not shown) at approximately 40–46 grams per day but is lower for the model with neither misclassification error (26 g). The nadir of all-cause mortality risk is shown for each model at very low levels of consumption: about half a drink per day in the pooled and biased groups and only 2 grams per day in the model containing neither error. The curve for the model containing neither error seems closer to an increasing dose–response relationship than a J-shape showing a small but non-significant protective effect. All models find a higher risk of very occasional drinkers relative to light drinkers and the scatter plots clearly illustrate the lack of homogeneity across study results.

CHD mortality

Figure 2 shows the results of categorical drinking group models. The pooled abstainer group model and the Former and Occasional Drinker Misclassification Errors model (containing the majority of studies) find the previously reported significantly reduced risk of CHD for light, moderate and heavier drinkers. The model including studies with only Former Drinker Misclassification Error shows a similar pattern but none of the results are statistically significant. A very different pattern is suggested by the model including the two studies with no misclassification error. Here estimated odds ratios are one or higher for all groups and no drinking groups are at significantly reduced (or increased) risk for CHD mortality.

Continuous models (Figure 3) show that occasional drinkers are more likely to die of CHD than lighter drinkers. The pooled abstainer group model finds reduced mortality risk at all levels of drinking with significant ($p < 0.01$) coefficients for logged alcohol volume, consistent with the conclusion that drinking protects against CHD mortality risk (with the exception of the occasional drinkers). In contrast, the model utilizing long-term abstainers



[1] In pooled model, former drinkers are statistically significantly higher than light drinkers.
[2] In pooled model, occasional drinkers are statistically significantly higher than light drinkers.
* In some studies Former Drinker Misclassification Errors were found but these studies classified some of their respondents as former drinkers.This accounts for the category of former drinker in these models. The number of observations for former drinkers in the studies containing both former drinker and occasional drinker misclassification is 1. The number of observations for former drinkers in the studies containing former drinker misclassification error only is 2.

Figure 2. Categorical drinking group models for CHD mortality.

without misclassification errors finds a significant ($p < 0.01$) J-shaped relationship between drinking amount and CHD mortality but the nadir of risk (at about 11 g/day) is equal to the risk for never drinking and the risk for CHD mortality is increased with heavier drinking. All graphs illustrate the considerable cross-study heterogeneity.

Adjusting for critical variables in individual studies

The influence of study characteristics did not alter the basic results indicating that the presented models are robust to these adjustments. However, adjustment for some variables in individual studies is critical. Additional analyses for samples age 35 or older at first measurement indicated similar results to the entire sample. Smoking status altered the results but only among heavier drinkers. Heavier

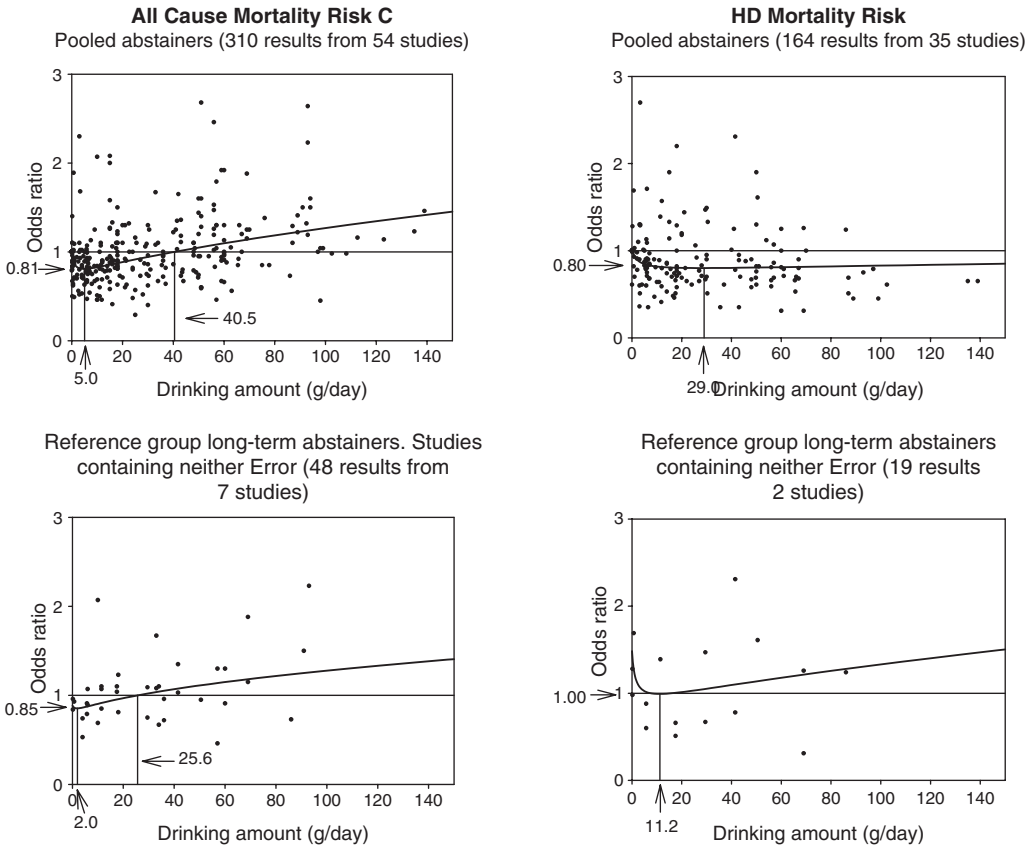


Figure 3. Continous models for all-cause and CHD mortality risk. Pooled abstainers model and model for studies containing neither error. Drinking amount in grams per day. All abstainers and former drinkers (when specified) set to zero. Significant relationships are found in the pooled abstainer models and not found in the long-term abstainer models.

drinkers who also were current smokers had twice the risk of dying than those who did not smoke, supporting evidence regarding the increase in mortality due to the dual effects of heavier drinking and smoking (Ferrence & Kozlowki, 1995).

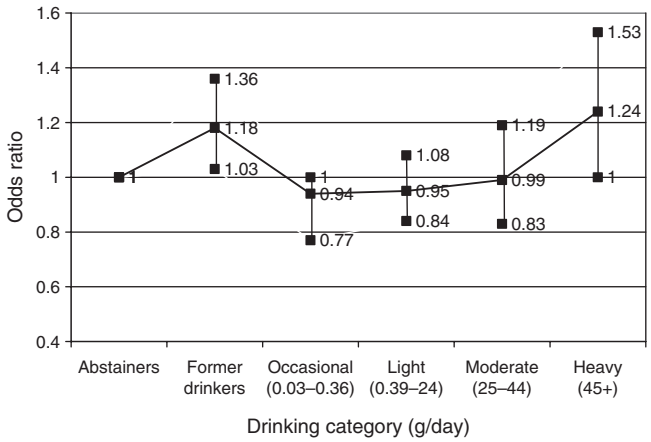
Possible misclassification

We separated studies that may have only partially contaminated the abstainer category with former drinkers. Results justified grouping potentially misclassified studies with those shown in the results above.

Introduction of the errors into error-free studies

We reconstructed the protective effect by introducing the classification errors into the error-free studies for all-cause mortality risk (Figure 4). When these studies are free from both potential sources of error, there is no *significant* protective effect. When the Former and Occasional drinkers are introduced into the abstainer group, a significant protective effect for light drinking is produced.

(a) Studies without Former or Occasional drinker Error.



(b) Studies without errors when former drinkers and occasional drinkers are combined with long-term abstainers.

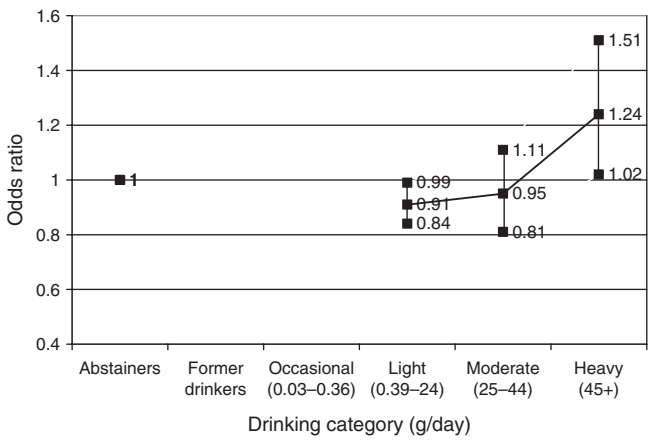


Figure 4. The effect of altering the long-term abstainer category in studies absent of both errors by combining former and occasional drinkers with long term abstainers. Categorical models for all cause mortality risk. Drinking categories are expressed in terms of grams per day.

This suggests that when sufficiently large portions of persons in ill health are included in the abstainer category, an apparent protective effect is created.

Discussion

Past reviews have concluded that the largely consistent findings from highly diverse studies indicate robust support for a protective effect because random error has been reduced in replication. However, systematic error is due to *consistently* applied faulty measurement. The postulated error (in this instance produced from misclassification) has been hidden from view because most studies combined former drinkers with abstainers and approximately half of these also combined occasional drinkers with abstainers thereby possibly including more individuals with some pre-existing illness in that category.

The contrast between the least biased group of studies to the larger group of more biased studies is consistent with the well-documented observation that as people age they both abstain and cut down to very occasional drinking for health reasons, disability, frailty and/or medication use. If they are included as ''abstainers'' in these studies then these ''abstainers'' will appear to be less healthy than light drinkers and at increased risk of premature death. In other words, regular light drinking may be a marker for good health among middle aged and older people, not a cause of it. As a consequence, estimates of the extent of the impact of cardiac benefits from light alcohol consumption on mortality risk may have been greatly over-estimated in previous meta-analyses (e.g. English et al., 1995; Maclure, 1993).

We acknowledge weaknesses in our study. (i) Rival hypotheses are difficult to test in associational epidemiological research because the data are often sufficiently unreliable to test and choose amongst hypotheses and clear mathematical representation of any putative hypotheses is typically crude (e.g., underestimation of consumption in population studies is well known (Potter, 1997)). (ii) Results are only suggestive because they cannot meet precise operational specification required to settle the matter of the potential existence of a cardiac protective effect. (iii) The lack of significance for light drinkers among the rare studies where abstainers are properly classified may be due to the lack of statistical power as much as to the possibility of systematic error. (iv) Some abstainers may self-select not to drink for factors unrelated to failing health and may be vulnerable to biochemical deficiencies putting them at increased CHD risk. (v) Although introduction of study-level confounders did not alter the findings, the *degree* and *precision* of adjustment across studies were not evaluated. For example pack years of smoking is rarely measured in these studies (Rothman & Greenland, 1998) and the statistical control for the key factor of age varies in quality.

Future testing of our general hypothesis should be carried out for prospective morbidity and case control studies of both morbidity and mortality. Greater attention in individual studies should be paid to the time ordering and specificity of symptoms that precede reduction or termination of alcohol consumption, transforming purely associational investigations to inquiries that explicitly evaluate the sequencing of these events. Only two studies were free from the postulated errors for CHD mortality. Future prospective studies should use far greater precision in their assessment of drinking behavior and abstinence so that the Shaper et al., alternative hypothesis can be further evaluated.

The present findings should give pause before accepting the major importance of cardiac protection from light alcohol use at the population level as a factor to be taken account in policy directives and clinical practice. Consideration should be given to studies of other health consequences reporting a ''protective effect'', e.g., dementia (Ruitenberg et al., 2002) and cognitive function (Peele & Brodsky, 2000), type 2 diabetes (Zilkens & Puddey, 2003), active *Helicobacter pylori* infection (Brenner, Rothenbacher, Bode, & Adler, 1997) and even the common cold (Takkouche et al., 2002).

Perhaps the most important implication of this exercise is for epidemiological scientific investigations in general. In 1988 – the same year Shaper et al., cautioned the scientific world that there was a significant potential error in prospective studies evaluating alcohol and CHD mortality risk – Feinstein published a strong critique of these studies in general (Feinstein, 1988). He stated: ''In the epidemiologic substitutes for experiment, the research methods seldom have the precautions, calibrations, and relative simplicity that are taken for granted in other branches of science.'' He asked us to proceed with caution, use our common sense and evaluate these studies with scientific principles in mind. It is in the spirit of his plea that this meta-analysis was performed.

Contributions of authors: Contributions of authors are as follows. Kaye M. Fillmore has taken primary responsibility for the research insofar as conceptualization and organization and William Kerr, Tim Stockwell, and Tanya Chikritzhs contributed to the development of the research plan, interpretation of results, and writing of various drafts. Alan Bostrom has been responsible for statistical analysis. In all respects, this has been a team effort with all authors contributing to the conception, design, analyses, and interpretation of the data. Each author has approved of the final draft and fulfilled the criteria of authorship; no person who has fulfilled the criteria of authorship has been excluded.

Competing interest statement: All authors declare no competing interests.

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Human subjects/ethics: This research project was conducted primarily at the University of California, San Francisco. The research design was approved by the human subjects committee overlooking all research endeavors.

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Appendix

Table AI. The studies: Source, country, date of Time 1 measurement, length of follow-up, sample type, total sample *N*, gender and age of subjects at Time 1, exclusions in sampling or analysis and abstainer group classification by outcome variable evaluated. Classification of misclassification errors: Errors 1 (former drinker misclassification) & 2 (occasional drinker misclassification), Error 1 but not Error 2, Neither Error.

Source	Country; date of T1 measurement; length of follow-up; sample type; total sample *N*	All cause mortality	CHD mortality
Andreasson & Brandt **Swedish Twin Study** [1]	Sweden; 1973; 15 years; registry of twins; $N=9057$	Men, age 18–67; Women, age 18–67; No exclusions; Error 1 but not Error 2	
Berberian et al. **The EOPZ Study** [2]	Netherlands; 1977; 10 years; general population of one town; $N=1620$	Men, 20+; Women 20+ No exclusions; Error 1 but not Error 2	
Boffetta & Garfinkel for men; Garfinkel et al. for women **American Cancer Society Study I** [3,4]	US 1959; 12 years; national volunteer convenience sample; $N=858{,}123$	Men, age 40–59; Women, age 30+; Excludes poor health and chronic disease for men; excludes breast cancer for women; Errors 1 & 2	Men, age 40–59; Women, age 30+; Excludes poor health and chronic disease for men; excludes breast cancer for women; Errors 1 & 2
Brenner et al. **German Construction Worker Study** [5]	Germany 1986–1988; 6 years; construction workers who underwent occupational health examinations in 6 health centers;; $N=6689$	Men, age 25–64; No exclusions; Error 1 but not Error 2	
Britton & Marmot, **Whitehall II Cohort Study** [6]	UK; 1985–1988; 11 years; civil servants aged 35–55 in 20 London-based departments; $N=10{,}308$	Men, age 35–55; Women, age 35–55; No exclusions; Error 1 but not Error 2	
Brunswick (reported in Leino et al. **Harlem Youth Study** [7,8][1]	US; 1975; 8 years; non-Hispanic blacks living in Central Harlem, New York City; $N=351$	Men, age 18–23; No exclusions; Neither Error	
Cahalan & Room (reported in Leino et al.) **US National Study 1969** [7,8][1]	US; 1969; 4 years; national sample of males; $N=978$	Men, age 21–69; No exclusions; Error 1 but not Error 2	
Cahalan & Room (reported in Leino et al.) and Fillmore et al.) **US National Study 1967** [8–10][1]	US; 1967; 7 years; national sample; $N=608$	Men, age 21+; Women, age 21+; No exclusions; Error 1 but not Error 2	

(*continued*)

Table AI. Continued.

Source	Country; Date of T1 measurement; length of follow-up; sample type; total sample N	All cause mortality	CHD mortality
Camacho et al. **The Alameda County Study** [11]	US; 1965; 15 years; general population of 1 California county; $N=4590$	Men, age 35+; Women, age 35+; No exclusions; Errors 1 & 2	Men, age 35+; Women, age 35+; No exclusions; Errors 1 & 2
Carmelli et al. **The Veterans' Twin Study** [12]	US; 1967–1969; 24 years; birth certificate search of White male multiple births between 1917–1927; $N=13{,}577$	Men, age 41–51; No exclusions; Error 1 but not Error 2	
Colditz **The Massachusetts Elderly Study** [13]	US; 1976; 5 years; statewide probability sample; $N=1271$	Men & women combined, age 66+; No exclusions; Error 1 but not Error 2	
Criqui et al. **Lipid Research Clinics Follow-up Study** [14]	US; 1972–1976; 9 years; medical practice sample; $N=7461$		Men, age 30+; Women, age 30+; Excludes angina or use of angina medication, use of antiarrhythmic agents, digitalis or propranolol, congestive heart failure, resting electrocardiogram arrhythmia, resting electrocardiogram evidence of m.i.; women using estrogen; Errors 1 & 2
Crowley (reported in Leino et al.) **US National Youth Study** [8,15]	US; 1982; 4 years; national sample with supplementary samples of blacks, Hispanics, economically disadvantaged non-black and Hispanic and young males in the military; $N=12{,}686$	Men, age 17–25; No exclusions; Error 1 but not Error 2	
Cullen et al. **The Brusselton Study** [16]	Australia; 1966; 23 years; General population of one town in Western Australia; $N=2171$	Men, age 40+; Women, age 40+; Excludes smokers; Error 1 but not Error 2	Men, age 40+; Women, age 40+; Excludes smokers; Error 1 but not Error 2
Deev et al. **Russian & US Collaborative Studies** [17]	Russia; 2 samples from 2 cities; one in 1975–1977, the other 1978–1982; average of 13 years. US: recruits to 12 clinics; 13 years. $N=4153$ in Russia; $N=4011$ in US	Russian women, age 40–69; Russian men, age 40–59; US women, age 40–69; US men, age 40–59; No exclusions; Error 1 but not Error 2	

Delabry et al. **Normative Aging Study** [18]	US; 1973; 12 years; volunteers from greater Boston area; $N=1823$	Men, 28–82; Excludes those with chronic disease, high blood pressure; Errors 1 & 2.	Men, 28–82; Excludes those with chronic disease, high blood pressure; Errors 1 & 2.
Doll et al. **British Physicians Study** [19]	UK; 1978; 13 years; British male physicians; $N=12{,}321$	Men, age 48–78; Excludes previous disease; Errors 1 & 2	Men, age 48–78; Excludes previous disease; Errors 1 & 2
Dyer et al. **Western Electric Company Study** [20]	US; 1957; 17 years; white men in one electric company; $N=1832$	Men, age 40–55; No exclusions; Errors 1 & 2	
Farchi et al. **Italian Study** [21]	Italy; 1965; 30 years; 2 villages; $N=1536$	Men, age 45–59; No exclusions; Errors 1 & 2	
Friedman & Kimball **Framingham Study** [22]	U.S; 1950; 24 years;. general population of 1 town; $N=4745$	Men, age 30–59; Women, age 30–59; Excludes smokers; Errors 1 & 2	Men, age 30–59; Women, age 30–59; Excludes smokers; Errors 1 & 2
Fuchs et al. **Nurses' Study** [23]	US; 1980; 12 years; national sample of registered nurses; $N=85{,}709$	Women, age 34–39; Women, age 40–49; Women, age 50–59; Women, age 60+; Excludes those with 10 or + food items left blank or implausible high or low scores for total food intake, history of cancer (except nonmelanoma skin cancer), angina, m.i. or stroke and those who greatly decreased alcohol intake in previous 10 year; Error 1 but not Error 2	Women, age 34–59; Excludes those with 10 or + food items left blank or implausible high or low scores for total food intake, history of cancer (except nonmelanoma skin cancer), angina, m.i. or stroke and those who greatly decreased alcohol intake in previous 10 year; Error 1 but not Error 2
Gaziano et al. **Physicians Study** [24]	US; 1982–1983; 5 years; male physicians in the US; $N=89{,}299$	Men, age 40–84; Excludes MI, stroke, cancer, liver disease; Errors 1 & 2.	Men, age 40–84; Excludes MI, stroke, cancer, liver disease; Errors 1 & 2
Goldberg et al. **Honolulu Heart Study** [25].	US; 15 years; Japanese males living in Hawaii; recruitment from general population; $N=6069$	Men, age 51–64; Men, age 65–75; Excludes CHD, CVD, cancer; Error 1 but not Error 2	Men, age 51–64; Men, age 65–75; Excludes CHD, CVD, cancer; Error 1 but not Error 2
Gordon & Doyle **The Albany Study** [26]	US; 1953; 18 years; civil service employees of one city; $N=1910$	Men, age 38–55; Excludes smokers; Errors 1 & 2	Men, age 38–55; Excludes smokers; Errors 1 & 2
Gronbaek et al. **The Combined Danish Study** [27]	Denmark; 1964–1976; 25 years; multiple samples: general population of city, employees in 14 companies; recruitment for heart study; $N=24{,}523$	Men & women combined, age 29–98; No exclusions; Errors 1 & 2	Men & women combined, age 29–98; No exclusions; Errors 1 & 2

(*continued*)

Table AI. Continued.

Source	Country; Date of T1 measurement; length of follow-up; sample type; total sample N	All cause mortality	CHD mortality
Hart et al. **Scottish Employed Men's Study** [28]	Scotland; 1970–1973; 21 years; Employees from various workplaces in 3 towns; $N=5766$	Men, age 35–64; No exclusions; Errors 1 & 2	Men, age 35–64; No exclusions; Errors 1 & 2
Hoffmeister et al. **German Cardiovascular Prevention Study** [29]	Germany; 1985, 1988; 7 years; general population surveys of Berlin-Spandau area; $N=7228$	Men, age 29–65; Women, age 29–65; Excludes liver disease; Errors 1 & 2	
Keil et al. **German MONICA Study** [30]	Germany; 1984; 8 years; probability sample of one city and two counties; $N=1071$	Men, age 45–64; Women, age 45–64; No exclusions; Errors 1 & 2	
Kittner et al. **Puerto Rico Study** [31]	Puerto Rico; 1965–1968; 12 years; General population sample; $N=9150$	Men, age 35+; No exclusions; Errors 1 & 2	Men, age 35+; No exclusions; Errors 1 & 2
Kivela et al. (1989) **Aging and Aged Study** [32]	Finland; 1974; 10 years; age cohort in 2 rural communities; $N=1112$	Men, age 55–74; Excludes MI, angina pectoris, atrial fibrillation or horizontal or downward sloping S-T sement depression of at least 0.5 mm or signs of pulmonary, rheumatic or syphilitic health disease; Errors 1 & 2	Men, age 55–74; Excludes MI, angina pectoris, atrial fibrillation or horizontal or downward sloping S-T sement depression of at least 0.5 mm or signs of pulmonary, rheumatic or syphilitic health disease; Errors 1 & 2
Klatsky et al. **Kaiser Study I** [33]	US; 1964–1968; 10 years; members of a medical plan in two California cities matched by sex, race, smoking, age, examination date and drinking status; $N=8060$	Men & women combined, age 40+; No exclusions; Error 1 but not Error 2	Men & women combined, age 40+; No exclusions; Error 1 but not Error 2
Klatsky et al. **Kaiser Study II** [34]	US; 1978–1985; 20 years; members of a medical plan in two California cities; $N=128{,}934$	Men, age 21+; Women, age 21+; No exclusions; Errors 1 & 2	Men, age 21+; Women, age 21+; No exclusions; Errors 1 & 2
Kono et al. **Japanese Physicians Study** [35]	Japan; 1965; 13 years; physicians in 17 prefecture medical associations; $N=5139$	Men, age 25+; No exclusions; Errors 1 & 2	Men, age 25+; No exclusions; Errors 1 & 2
Kozarevic et al. **Bosnia/ Croatia Study** [36]	Yugoslavia; 1964–1965; 7 years; General population of 1 town in Bosnia and 1 in Croatia; $N=10{,}398$		Men, age 37–62; No exclusions; Errors 1 & 2

Liao et al. **NHIS Study** [37]	US; 1989; 6 years; national general population; $N = 43{,}695$	Men, age 40+ Women, age 40+; No exclusions; Neither Error	Men, age 40+; Women, age 40+; Excludes CHD; Neither Error
Malyutina et al. **The Novosibirsk Study** [38]	Russia; 1985/86, 1988/90, 1994/95; 9 years; three surveys (some random) and one pilot study in Novosibirsk; $N = 6502$	Men, age 25–64; No exclusions; Error 1 but not Error 2	Men, age 25–64; No exclusions; Error 1 but not Error 2
Marmot et al. **Whitehall Civil Servants Study** [39]	UK; 1967–1969; 10 years; male civil servants in several departments in London; $N = 1422$	Men 40–64; No exclusions; Errors 1 & 2	
Maskarinec et al. **Multiethnic Hawaiian Study** [40]	US; 1975–1980; 20 years; general population of Hawaii; $N = 27{,}678$	Men, age 30+; Women, age 30+; Excludes cancer; Errors 1 & 2	Men, age 30+; Women, age 30+; Excludes cancer; Errors 1 & 2
Mertens et al. **Health Services Study** [41]	US; 1987; 4 years; recruited sample for health services settings but not from alcohol treatment programs; $N = 1760$	Men & women combined, age 55–65; Excludes lifetime abstainers; Error 1 but not Error 2	
Miller et al. **Trinidad Study** [42]	Trinidad; 1977; 8 years; general population; $N = 1341$	Men, age 35–69; No exclusions; Errors 1 & 2	Men, age 35–69; Excludes ischaemic heart pain, or medical history cardiac disease except uncomplicated hypertensive heart disease; Errors 1 & 2
Paunio et al. **ATBC Study** [43]	Finland; 1894–1988; 7 years; general population of men in south & west Finland who smoked at least 5 cigarettes per day; a randomized clinical trial to explore the efficacy of a-tocopherol and B-carotene supplements. Only participants in the placebo group are utilized in this study; $N = 7052$.	Men, age 50–69; Excludes, malignancy (not nonmelanoma skin cancer or carcinoma in situ, unstable angina pectoris, chronic renal insufficiency, cirrhosis, chronic alcoholism, anticoagulant therapy, use of vitamins E, A or beta-carotene supplements, use of anticoagulants; Error 1 but not Error 2	Men, age 50–69; Excludes, malignancy (not nonmelanoma skin cancer or carcinoma *in situ*, unstable angina pectoris, chronic renal insufficiency, cirrhosis, chronic alcoholism, anticoagulant therapy, use of vitamins E, A or beta-carotene supplements, use of anticoagulants; Error 1 but not Error 2
Rehm et al. **Alcohol Research Group Study** [44]	US; 1984; 11 years; general population sample; $N = 5072$	Men, age 18+; Women, age 18+; Excludes all ethnic groups other than, black, Hispanic or white; Neither Error	
Rehm et al. **Upper Bavarian Study** [45]	Germany; 1975–1977; 13 years; general population sample of a rural Bavarian community; $N = 1668$	Men, age 30–69; Women, age 30–69; No exclusions; Errors 1 & 2.	

(*continued*)

Table AI. Continued.

Source	Country; Date of T1 measurement; length of follow-up; sample type; total sample N	All cause mortality	CHD mortality
Renaud et al. **French Study** [46]	France; 1978–1983; 13 years; consecutive health center patients; $N=34{,}014$	Men, age 40–60; No exclusions; Errors 1 & 2	Men, age 40–60; No exclusions; Errors 1 & 2
Rimm et al. **Health Professionals Study** [47]	US; 1986; 2 years; national sample of health professionals; $N=44{,}059$		Men, age 40–75; Excludes those not reporting average daily food intake of 3.35–17.6 MJ and did not eat more than 70 food items, cancer (except non-melanoma skin cancer), m.i., angina, stroke, PTCA or CABG; Errors 1 & 2
Romelsjo & Leifman **Swedish Conscript Study** [48]	Sweden; 1969; 25 years; Military conscripts; $N=49{,}618$	Men, age 17–19; No exclusions; Error 1 but not Error 2	
Salonen et al. **Eastern Finland Study** [49][1]	Finland; 1972; 7 years; general population of men in 2 counties in Eastern Finland; $N=4458$	Men, age 30–59; Excluded those with prior AMI or angina pectoris in last 12 months; Errors 1 & 2	Men, age 30–59; Excluded those with prior AMI or angina pectoris in last 12 months; Errors 1 & 2
San Jose et al. **GLOBE Study** [50]	The Netherlands; 1991; 5 years; general population from 17 communities; $N=17{,}898$	Men & women combined, age 14–74; No exclusions; Error 1 but not Error 2	
Scherr et al. **The EPESE Study** [51]	US; 1981–1983; 5 years; 3 general population samples of those age 65+ in East Boston, Massachusetts, New Haven, Connecticut and rural counties in Iowa; $N=10{,}293$	Men & women combined, Iowa age 65+; Men & women combined, E. Boston, age 65+; Men & women combined, New Haven, age 65+; Excludes m.i, stroke or cancer; Error 1 but not Error 2.	
Semenciw et al. **Nutrition Canada Survey** [52]	Canada; 1970–1972; 10 years; national general population sample + some unsolicited volunteers; $N=16{,}090$.		Men, age 35–79; Women, age, 35–79; Excludes heart disease and stroke; Errors 1 & 2

Serdula et al. **NHANES Study** [53]	US; 1971–1975; 14 years; national general population sample; $N=8,187$	Men, age 40–64; Men, age 65+; Women, age 40–64; Women, age 65+; Excludes heart failure, heart attack, high blood pressure, stroke, diabetes, malignant tumor or growth, chronic bronchitis or emphysema, hepatitis, kidney disease or kidney stone; Error 1 but not Error 2	Men, age 40–64; Men, age 65+; Women, age 65+; Excludes heart failure, heart attack, high blood pressure, stroke, diabetes, malignant tumor or growth, chronic bronchitis or emphysema, hepatitis, kidney disease or kidney stones; Error 1 but not Error 2
Shaten et al. **MRFIT Study** [54]	U.S; 1973–1975; 11 years; intervention trial for CHD; $N=12,866$		Men, age 35–57; Excludes those not in the upper 10% of CHD risk using Framingham criteria, heavy alcohol users and smokers; Errors 1 & 2
Simons et al. **Dubbo Study** [55]	Australia; 1988–1989; 10 years; general population of Dubbo, New South Wales born before 1930; $N=3105$	Men, age 60+; Women, age 60+; No exclusions; Error 1 but not Error 2	
Suhonen et al. **Social Insurance Study** [56]	Finland; 1973–1976; 5 years; 12 cohorts from 4 regions in re-examination of the Social Insurance Institution's Mobile Clinic Health Survey; $N=4532$	Men, age 40–49; Men, age 50–59; Men, age 60–64; No exclusions; Error 1 but not Error 2	Men, age 40–49; Men, age 50–59; Men, age 60–64; No exclusions; Error 1 but not Error 2
Temple & Leino (reported in Leino et al. and Fillmore et al.) **San Francisco 1964 Study**) [57,8,10][1]	US; 1964; 20 years; general population San Francisco, CA; $N=970$	Men, age 23–88; Women, age 23–88; No exclusions; women analyzed only – too few abstaining deaths for men Error 1 but not Error 2	
Temple & Leino Reported in Leino et al. **San Francisco Study** 1967) [57,8][1]	US; 1967; 17 years; general population of white males, San Francisco, CA; $N=786$	Men, age 21–59; No exclusions; Error 1 but not Error 2	
Theobald et al. **Stockholm County Study** [58]	Sweden; 1969–1970; 26 years; general population sample of Stockholm County; $N=28,001$	Men, age 18–65; Women, age 18–65; No exclusions; Errors 1 & 2	Men, age 18–65; Women, age 18–65; No exclusions; Errors 1 & 2
Thun et al. **American Cancer Society Study II** [59]	US; 1982; 9 years; national volunteer sample; $N=490,000$	Men & women combined, age 30–59; Men & women combined, age 60–79; Excludes heart disease, hypertension, use of medications for these, stroke, diabetes; Errors 1 & 2	Men, age 30–104; Women, age 30–104; Excludes heart disease; Errors 1 & 2

Table AI. Continued.

Source	Country; Date of T1 measurement; length of follow-up; sample type; total sample *N*	All cause mortality	CHD mortality
Tsugane et al. **JPHC Study** [60]	Japan; 1990; 6 years; General population of 14 administrative districts; *N* = 19,231.	Men, age 40–59; Excludes cancer, CVD, MI, liver disease; Errors 1 & 2	
Tsubono et al. **Rural Japanese Study** [61]	Japan; 1988; 4 years; general population of Wakuya; *N* = 4318.	Men & women combined, age 40+; No exclusions; Neither Error	
Tsubono et al. **Miyagi Study** [62]	Japan; 1990; 7 years; general population of men in Miyagi Prefecture; *N* = 21,593.	Men, age 40–64; Excludes cancer, CHD, stroke, liver disease, Diabetes & deaths in 1st 2 years of follow-up; Neither Error	
Wannamethee & Shaper **British Regional Heart Study** [63]	UK; 1984; 8 years; Random sample for 1 general practice in 24 British towns; *N* = 7167	Men, age 45–64; No exclusions; Neither Error	Men, age 45–64; No exclusions; Neither Error
Wilsnack et al. Reported in Fillmore et al. **US National Sample** [64,10]	US; 1981; national stratified (by drinking) probability sample; *N* = 911	Women, age 21+; No exclusions; Error 1 but not Error 2	
Yuan et al. **Chinese Study** [65]	China; 1986–1989; 6 years; General population of 4 areas in Shanghai; *N* = 18,244	Men, age 45–64; Excludes former drinkers. Errors 1 & 2.	Men, age 45–64; No exclusions; Unique group because contaminates drinkers with former drinkers. Errors 1 & 2

[1]Excluded from analysis.

Table AII. Proportion study results for study characteristics by all-cause and CHD risk.

Study characteristics	All-cause	CHD
A. Structural characteristics		
Gender		
Male	57	65
Female	30	26
Both	13	9
Youngest age		
<30	26	19
30–39	21	33
40–49	35	34
50–59	6	5
60+	12	9
Oldest age		
<50	5	1
50–59	17	16
60–69	31	28
70+	47	55
Median age		
<40	3	0
41–50	31	30
51–60	33	30
61–70	23	32
71+	10	8
Country		
Australia	4	3
Canada	0	2
China	2	1
Denmark	1	2
France	2	2
Finland	4	5
Germany	7	3
Japan	6	2
Italy	1	2
Netherlands	3	3
Puerto Rico	1	2
Russia	4	5
Sweden	5	2
Trinidad	1	1
United Kingdom	8	6
United States	51	58
Yugoslavia	0	2
Sampling frame		
General population or community	60	55
Age cohort	5	7
Occupational group	17	15
Medical practice	7	11
Volunteer/convenience	7	10
Other	4	2
Total sample size		
2499 or <	26	25
2500–10,999	39	38
11,000–15,999	3	4
16,000–19,999	4	1
20,000–29,999	11	13
30,000 or >	18	19

(*continued*)

Table AII. Continued.

Study characteristics	All-cause	CHD
Date of study (Time 1)		
1950–1959	8	11
1960–1969	17	20
1970–1979	27	34
1980–1989	42	33
1990–1999	6	2
Length of follow-up		
5 years or <	13	13
6–10 years	30	33
11–15 years	31	26
16–20 years	15	15
21+ years	11	13
% having 31% or >T1 sample loss (e.g., refusal or non-response)	17	21
ICD code used v. judgment based on records/family reports	–	67
Method of analysis proportional hazard	65	54
B. Exclusions		
Excludes/stratifies smokers from analysis	5	9
Excludes/stratifies CHD/other illnesses from analysis	25	33
C. Alcohol measure characteristics		
Pattern of drinking		
Frequency only	4	9
Quantity only	13	13
Self-classification	2	3
Frequency + quantity	44	33
Typical volume	19	24
Number drinks/day	2	2
Number drinks/week	8	10
Number of drinks/month	4	2
Number drinks/day for daily or almost daily drinkers	1	2
# drinks last 3 days	2	1
# drinks last month	1	1
Time frame for assessing abstinence		
24–48 h recall	2	4
3 day recall	3	1
1 week recall	0	3
1 month recall	1	1
1 year recall	30	29
30 year recall	1	2
Usual drinking or current	27	19
Number of drinks per day or daily drinking	4	3
Daily drinking in a week	0	2
Weekly drinking	12	13
Monthly drinking	6	7
Lifetime drinking	14	16
Time frame for assessing drinking		
24–48 h recall	2	4
3 day recall	3	1
1 week recall	7	13
2 week recall	2	5
1 month recall	8	8
1 year recall	18	12
30 year recall	1	2
Usual drinking or current	28	21
Number of drinks per day or daily drinking	11	11

(*continued*)

Table AII. Continued.

Study characteristics	All-cause	CHD
Daily drinking in a week	0	2
Weekly drinking	13	14
Monthly drinking	7	7
D. Adjusted variables in model (% *yes*)		
Age	98	97
Gender (for studies combining men & women in results)		
Smoking	84	76
Past heart problems	24	17
Past stroke	15	12
Diabetes	27	21
General health	24	4
Chronic bronchitis	6	6
MI in parent(s)	6	3
Hypertension	29	28
Blood pressure	33	31
Serum cholesterol	24	25
Forced expiratory volume	7	3
Serum triglicerides	2	4
Left ventricular hypertrophy	7	7
HDL	15	16
LDL	15	16
BMI	49	46
Uric acid	2	4
Hemoglobin	3	5
Aspect of diet	11	7
Exercise	29	29
Skin fold	2	2
Disability	9	9
Use of aspirin	6	5
Use regular medications	4	2
Estrogen/hormone replacement therapy for studies including women	17	10
Oral contraceptives for studies including women	10	6
Menopausal status for studies including women	10	6
Aspect of mental status	14	9
Measure of social class	55	46
Race/ethnicity	29	22
Marital status	13	10
Measure of social isolation	6	3
E. Aggregate or semi-aggregate measures		
Ratio abstainers/drinkers		
0.01–0.20	29	34
0.21–0.40	25	20
0.41–0.70	22	22
0.71–0.99	9	9
1.00–6.69	15	15
Per capita consumption of alcohol at Time 1 of study		
1.99–2.37	16	18
2.38–2.67	17	15
2.68–5.00	23	28
5.01–6.90	18	16
6.91–14.40	26	21

(*continued*)

Table AII. Continued.

Study characteristics	All-cause	CHD
Standardized CHD mortality rates age 45+ for men at Time 1		
130–429	9	6
430–729	14	12
730–1029	32	26
1030–1394	45	56
Standardized mortality CHD rates age 45+ for women at Time 1		
74–247	10	6
248–421	23	12
422–594	44	50
595–771	23	32
Standardized all cause mortality rates per 100,000 men age 15+ at Time 1		
820–1019	9	2
1020–1219	48	43
1220–1419	24	30
1420–1639	19	25
Standardized all cause mortality rates per 100,000 women age 15+ at Time 1		
467–669	38	30
670–779	27	26
680–1079	34	41
1080–1182	1	1

Correction: The Crowley study and the Yuan et al. study were coded as ''neither error'' in Table AI.

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