Heavy Drinking Episodes and Heart Disease Risk

by

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Abstract

Background: The relationship between average alcohol consumption and heart disease is well researched, showing a substantial cardioprotective association. This dissertation examined the epidemiological evidence for an effect of heavy episodic drinking (HED) over and above the effect of average alcohol consumption on heart disease.

Methods: Electronic databases were systematically searched for epidemiological studies on the effect of HED on heart disease and identified articles were quantitatively summarized in a meta-analysis. Meta-regression models were used to examine the effect of characteristics of primary studies. Using individual-level data, semi-parametric Cox regression models were used to investigate HED exposure within narrow categories of average alcohol consumption in a US national population sample (n = 9,937) in relation to heart disease mortality in an 11-22 year follow-up. Frequency of heavy drinking episodes was used to identify latent classes of drinking history using growth mixture modeling in a sub-sample of this US cohort. Retrieved classes were used as independent variables in Cox regression models with heart disease mortality as the outcome event.
Results: A pooled relative risk of 1.45 (95% confidence interval (CI): 1.24-1.70) for HED compared with non-HED drinkers with average alcohol consumption between 0.1-60 g/day was derived in a meta-analysis. A strong and consistent association with HED was found among current drinkers consuming an average of 1-2 drinks per day in the US cohort. There was no evidence of increased heart disease mortality resulting from the frequency of heavy drinking episodes before the age of forty.

Conclusions: There is reasonable and consistent evidence for an association of HED and heart disease in current drinkers, negating any beneficial effect from alcohol consumption on heart health. History of frequency of heavy drinking episodes, however, showed no evidence for such an effect modification.
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List of Abbreviations

CES-D, Center for Epidemiologic Studies Depression Scale
IHD, ischaemic heart disease
HED, heavy drinking episodes
HDL, high-density cholesterol
LDL, low-density cholesterol
NAS, National Alcohol Survey
NDI, National Death Index
BMI, Body Mass Index
BIC, Bayesian Information Criterion
AIC, Akaike Information Criterion
Chapter 1: Introduction and Objectives

1.1 Background
Alcohol consumption, related to some 60 diseases and conditions (1, 2), has been found to be one of the most important risk factors for burden of disease worldwide, especially in developed countries (3). Most of the health effects of alcohol consumption are detrimental. However, for a few disease categories, most prominently ischaemic heart disease (IHD), most epidemiological studies estimated a beneficial effect for regular light to moderate intake of alcohol for incidence and mortality (4, 5). Evidence for a cardioprotective association dates back to the early part of the last century (6). Although showing a mostly positive and linear dose-response relationship with several other diseases (including several neoplasms (7) and hypertension(8)), the relationship of average daily alcohol consumption on heart disease has been shown to follow a curvilinear form, with a reduction in risk associated with low to moderate average daily consumers compared with non-drinkers and heavy drinkers (4, 5). Over the last two decades, however, research has shown that besides average daily consumption, another dimension of alcohol consumption has been identified to play a role in ischaemic heart disease risk: the pattern of consumption (9). More specifically, the proportion of the average intake attributed to heavy episodic drinking (often defined as 5 or more drinks, or about 50 to 60 g of pure alcohol, on one occasion) has been identified in heart disease risk, which was not accounted for in previous meta-analyses (5, 10). Average volume of drinking has been the focus of research on alcohol to date (11-13), although the potential importance of drinking patterns has long been recognized (14) and recently reinforced (15). Each of the major meta-analyses in this area have shown evidence of important heterogeneity across studies, and heavy drinking patterns may explain this
heterogeneity (5, 10). However, HED has not been addressed in these studies because in most of the larger cohort studies, patterns of heavy drinking were either not assessed or very rare (9).

Although hundreds of cross-sectional, case-control and cohort studies have examined the relationship between alcohol consumption and IHD risk, detailed knowledge of the effects of different drinking patterns and average alcohol consumption remains elusive, mainly due to: 1) lack of power in the few studies examining irregular drinking behaviour (small sample size, limited number of cases); 2) imprecision in exposure measurement (measured at baseline only, with no or varying assessment of pattern of drinking); and 3) selection bias (oversampling of relatively healthy subjects in stable living conditions) (16-18).

Furthermore, confounding due to some of the many risk factors for IHD cannot be excluded, which is a debate that has received much recent attention (19-21). Due to these methodological shortcomings, the beneficial effects of alcohol consumption, when only assessed as a daily average, may have been exaggerated or underestimated in the past, at least for some sub-populations. This is the subject of a recent debate in the scientific community (20-22). The distinction of whether intake is distributed over few drinking days with binge drinking episodes, or more regular consumption in moderate amounts, is very important from a biological perspective in terms of the likely health consequences.

**1.1.1 Short-term experimental evidence and potential pathways**

The strongest argument for a causal cardioprotective effect of alcohol consumption comes from biochemical evidence from experimental studies. Regular low to moderate amounts have been found to have beneficial effects on intermediate biomarkers for reduced risk of
heart disease (23, 24). In a dose-dependent manner, alcohol exposure has been shown to increase high density lipoproteins (HDL), inhibit platelet activation, lower levels of fibrinogen activity, and have anti-inflammatory effects [for reviews, please see (23-27)]. It has been estimated that approximately 50% of the beneficial effect of alcohol on heart disease risk is mediated through the aforementioned biochemical pathways (with an increase in HDL level being the most important mediator of IHD risk for regular non-heavy alcohol intake), resulting in a 25% reduction in IHD for an individual consuming 30 grams/day, relative to abstinence from alcohol (24). Binge drinking, on the other hand, has been found to be related to detrimental effects on the heart, including adverse effects on blood pressure, fibrinolytic factors and ventricular arrhythmia after binge drinking episodes (26). Evidence for the effect of binge drinking on lipid profiles is inconsistent. In contrast to regular moderate drinking, which raises HDL levels, a comprehensive review concluded that low density lipoproteins were increased by binge drinking episodes with no elevation in HDL levels, indicating an overall detrimental effect on the heart through lipid levels (28).

1.1.2 Measurement of alcohol exposure

Alcohol intake can be measured in many different ways (18, 29-32), and is often evaluated as number of drinks per week, or usual intake per drinking day and usual number of drinking days (Quantity-Frequency (QF) approach). From these measures, average daily amount of pure alcohol intake is calculated. The QF approach (average dose per reference period and usual frequency of drinking days, assessed as two items) is the crudest measure to capture any type of drinking pattern. Although this is, by far, the most widely used approach in alcohol epidemiology (17, 33), these methods leave ample room for many patterns of alcohol intake to yield the same average daily amount which might be consumed in a few binge
drinking days or via regular low daily amounts. Some epidemiologic studies have also sought to address heavy drinking occasions or episodes of ‘binge’ drinking and the definitions used have differed markedly across studies (26, 34, 35). To better define the dimension of drinking pattern, the term ‘heavy episodic drinking’ (HED) will be used from here on. This definition includes irregular (4 or less days per week) and heavy (5+ standard drinks, or >= 60 g pure alcohol/drinking day) occasions. It has been noted that among the many epidemiological studies examining the effect of alcohol consumption on IHD, only few included measures of alcohol consumption that allow for the identification of irregular heavy drinking occasions, and the separation of non-heavy regular drinkers from those with a pattern of HED within comparable levels of apparent average daily consumption (34). In fact, most studies only examined one dimension of consumption (i.e., average alcohol intake per day, regardless of drinking and non-drinking days (4, 5, 36, 37)), and have not taken into account the potential detrimental effect of irregular heavy drinking episodes (26, 38, 39).

1.1.3 Concurrent measurement of drinking volume and irregular heavy drinking occasions

Identifying the most valid, reliable and relevant measure for alcohol consumption can only be determined in relation to the specific goals of the study because no gold standard measure or biomarker for alcohol intake over the lifespan exists that satisfactorily addresses drinking patterns that are relevant for research on the diverse physiological and social effects of alcohol intake. Although reliability of self-reported alcohol consumption has been shown to be good (40, 41), the measurement of alcohol intake is complex, and based on accumulating evidence over the past two to three decades, has been described as involving three major dimensions: overall volume; frequency; and variability (42, 43). Comparisons of approaches
have shown that different measures result in inconsistencies in identifying mostly heavy drinkers as well as abstainers or light drinkers. Assessment of intake among regular, moderate drinkers is least affected by the type of measure (44, 45). Nevertheless, identifying the most appropriate reference group and dimensions among drinkers is crucial in determining the shape of the risk function of alcohol intake on heart disease risk.

Episodes of heavy drinking are also of interest to researchers who study other acute outcomes of alcohol intake, such as trauma. To be able to capture HED was the primary reason for the development of an alternative (to the QF method) measure of alcohol intake, namely the Knupfer-Series (KS), which incorporates questions about the proportion of occasions for several drinking levels (46-49) (sometimes also called a ‘graduated frequency scale’). The KS was first introduced in the 1967 US National Survey and the algorithm to derive overall volume and drinking frequency is complex. It was first mentioned by Cahalan (50) and described in detail by Room (43). The KS asks about frequency of drinking occasions and then about the proportion of several categories of drinks per occasion, all by type of beverage. The second part of the KS asks about the proportion of drinking occasions for a specific range of drinks per occasion (see Appendix A for original questionnaire items). Evidence for drinking patterns not distinguished by measures of average grams per day has long been recognized (51), and Gruchow (52) was one of the first to provide empirical evidence on the effect of variability of drinking pattern on coronary occlusion in patients referred to coronary arteriography while taking into account total alcohol intake. However, many other factors, such as length of reference period, the number of questions available in a questionnaire, willingness of the respondents to answer lengthy questionnaires, and most
prevalent drinking pattern in the respective population, have to be taken into account in determining the validity and relevance of measures to assess alcohol consumption. In general, beverage-specific questions (usual frequency of consumption and usual amount consumed for each of multiple beverage types) yielded a higher volume of intake measures (53, 54), as do measures of other forms, which include larger numbers of items (30, 55-57). A higher overall volume is often argued to be more valid because underreporting is substantial when survey volume is compared to adult per capita sales statistics (58, 59). Because the interest lies in variability of drinking events and the pattern of drinking, the reference period of past 12 months before the interview used in the analysis in chapters 3 and 4 seems appropriate (30, 60).

1.1.4 Change of alcohol consumption over the lifetime

Many people may change their consumption over the lifetime, which is not captured by using only baseline measurement of current alcohol consumption, the most common form reported in cohort studies or case-control studies. In an analysis of change of drinking volume (including abstainers) using three large US surveys with multiple measurements, Kerr and colleagues (61) showed that a substantial portion of drinkers, as well as those initially classified as abstainers, changed their last month’s overall volume of alcohol intake at subsequent measurements. Several studies reported movement over time between abstention groups and drinking groups (62-68); however, most change of intake occurred within 0-50 g/day, with less among abstainers or those consuming greater than 50 g/day (61, 62). As outlined in this chapter, imprecise measurement of average daily alcohol consumption, rare assessment of drinking pattern, and virtually no research on change of drinking pattern over time, have all made the interpretation of existing epidemiological studies of alcohol intake
and heart disease risk more difficult and left this body of literature prone to criticism on methodological grounds (20, 22, 67). Finally, most studies have not separated life-time abstainers from former drinkers. Former drinkers might have quit for health reasons and therefore have a higher baseline risk than true lifetime abstainers, which might lead to artificially raised risk in that comparison group (69, 70). The last point has crucial implications for the shape of the risk function (a cardioprotective effect implies that the risk of low to moderate alcohol consumption is lower compared to abstainers as the referent).

1.2 Objectives

1.2.1 Thesis outline

This doctoral thesis takes the form of three manuscripts, of which two have been published (71, 72). The first manuscript (chapter 2) is a systematic review of the literature on heavy drinking episodes (HED) on heart disease risk, including a meta-regression to quantify this effect (see Appendices B, C, D for additional data). The second and third manuscripts (chapters 3 and 4) comprise an original survival analysis using secondary data and investigated the influence of HED on heart disease mortality risk (see Appendix E for ICD codes), addressing many important limitations of previous studies as outlined above. The second manuscript (chapter 3) investigated the association of HED and heart disease mortality risk by separating several dimensions of alcohol consumption simultaneously (average daily alcohol intake, former drinking pattern, and current and past HED). There is limited knowledge on change of alcohol intake over the lifetime and virtually no research on HED over the lifetime with regard to heart disease mortality risk. The third analysis (chapter 4) used growth mixture modeling to identify latent classes of HED over the lifetime (see
Appendix F for original questionnaire items) and then relates these latent classes to heart disease mortality over the course of the follow-up period.

This thesis used the unique opportunity to investigate several dimensions of past and current alcohol consumption patterns with an analysis of the US National Alcohol Survey (NAS; National Institute on Alcohol Abuse and Alcoholism) and mortality data from the National Death Index (NDI). Specifically, these datasets allow for the analysis of 1) a detailed and accurate identification of irregular heavy drinking occasion at different levels of average daily alcohol intake (chapter 3), 2) accurate identification of a suitable comparison group in lifetime abstainers (chapter 3 and 4) 3) separation of former drinkers (chapters 2-4, and 4) retrospectively assessed change of HED over time (chapter 4). Furthermore, the NAS datasets contain detailed information on some of the most important potential confounders for the relationship of alcohol consumption on heart disease, such as tobacco and other drug use, depression and socio-demographic characteristics.

1.2.2 Research questions and hypotheses

The three research questions addressed in the three manuscripts (chapters 2-4) are described below.

**Research question 1)** As derived from a systematic review of published studies in the literature, what is the pooled relative risk of heart disease among irregular heavy drinkers compared to regular non-heavy drinkers?

**Research question 2)** What is the risk of mortality from heart disease among HED compared to lifetime abstainers and regular non-heavy drinkers in a nationally representative
US sample? More specifically, based on the review of the literature, the main hypotheses for this investigation were:

1) Compared to lifetime abstainers, drinkers with HED at low to moderate average daily alcohol intake will show no statistically significant beneficial effect on heart disease mortality.

2) Compared to lifetime abstainers, low to moderate average daily alcohol intake without HED will show a statistically significant beneficial effect on heart disease mortality.

3) Compared to low to moderate average daily alcohol intake without HED, low to moderate drinkers with HED will have a statistically significant increased risk of heart disease mortality.

**Research question 3)** How does the frequency of HED change over time and how do different patterns of change influence heart disease mortality risk?

**1.3 Involvement of the Author in the Thesis**

Using previously collected data the candidate developed the concept of the analyses, conducted the literature review, meta-analysis, and all statistical analyses. The candidate was responsible for all aspects of data management, data analyses and manuscript write-up. For papers 2 and 3, the candidate created a new dataset by merging two waves of the US National Alcohol Survey (linked to mortality data from the National Death Index, provided by the Alcohol Research Group, Appendix G). Manuscript drafts were presented to the committee and all co-authors, discussed, and the candidate took the lead in preparing the final manuscripts and submission to appropriate journals.
1.4 References


Chapter 2: Irregular Heavy Drinking Occasions and Risk of Ischemic Heart Disease: A Systematic Review and Meta-Analysis

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Headings were included to reflect the structure of this dissertation.
2.1 Abstract

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 (I² = 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.

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

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.

2.3 Material and Methods

2.3.1 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 (≥60 g of pure alcohol per occasion, or ≥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.

2.3.2 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).
2.3.3 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 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.

2.4 Results

2.4.1 Search results

The electronic search revealed 1,081 citations (Figure 2-1). 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 2-1 and 2-2 show characteristics of studies included in the quantitative part of the meta-analysis. Of the 14 articles 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.
Figure 2-1. 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.

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.
Figure 2-2. 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.

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.
Table 2-1 Characteristics of 10 Cohort Studies Selected for Quantitative Analysis of the Effect of Irregular Heavy Drinking Occasions on Ischemic Heart Disease Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>Alcohol Measurement</th>
<th>Sex</th>
<th>Incident No. of IHD Cases, Irregular Heavy Drinking/Non-heavy Drinking</th>
<th>Average Daily Alcohol Intake (Where Applicable)</th>
<th>Heavy Drinking Episode</th>
<th>Reference Category</th>
<th>Follow-up Time, Years</th>
<th>Age, Years</th>
<th>Country</th>
<th>Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolstrup et al. (49), 2006</td>
<td>Mortality (hospital discharge register) and mortality (cause of death register) (ICD-8 codes 410–414, ICD-10 codes I20–I25)</td>
<td>Typical drinking dose (1 standard drink = 12 g of ethanol)</td>
<td>W</td>
<td>9/52</td>
<td>7–13 days/week</td>
<td>≤1 day/week</td>
<td>5–7 days/week</td>
<td>5.7</td>
<td>50–65</td>
<td>Denmark</td>
<td>Age, education; smoking; physical activity; BMI, total intake of vegetables, fruit, fish, and saturated fat</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>M</td>
<td>31/90</td>
<td>7–13 days/week</td>
<td>≤1 day/week</td>
<td>5–7 days/week</td>
<td>5.7</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>M</td>
<td>52/90</td>
<td>14–20 days/week</td>
<td>≤1 day/week</td>
<td>5–7 days/week</td>
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<tr>
<td>Mäkelä et al. (43), 2005</td>
<td>Mortality (hospital discharge register) and mortality (cause of death register) (ICD-8 and ICD-9 codes 410–414, ICD-10 codes I20–I25)</td>
<td>Drinking episode leading to BAC &gt;0.1% (HED)</td>
<td>W</td>
<td>4/18</td>
<td>HED only</td>
<td>Mostly non-HED</td>
<td>14.4</td>
<td>25–69</td>
<td>Finland</td>
<td>Age, total alcohol intake, period, marital status, education, smoking</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>M</td>
<td>55/25</td>
<td>HED only</td>
<td>Mostly non-HED</td>
<td></td>
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<tr>
<td>Laatikainen et al. (42), 2003</td>
<td>Mortality (cause of death register) (ICD-9 codes 410–414, ICD-10 codes I20–I25)</td>
<td>Any heavy drinking episode (1 standard drink = 12 g of ethanol)</td>
<td>M</td>
<td>38/85</td>
<td>Any ≥6 drinks per beverage type in the past year</td>
<td>≤5 drinks per beverage type in the past year</td>
<td>5 years and 10 years</td>
<td>25–64</td>
<td>Finland</td>
<td>Age (continuous), average alcohol intake (g/week: 0–95.9, 96–199.9, ≥200), smoking (current vs. other), education (low, medium, high)</td>
<td></td>
</tr>
<tr>
<td>Mukamal et al. (51), 2003</td>
<td>Fatal and nonfatal MI (WHO criteria (26))</td>
<td>Drinking frequency within narrow categories of average total alcohol intake</td>
<td>M</td>
<td>173 combined</td>
<td>10–14.9 g</td>
<td>&lt;3 drinking days</td>
<td>≥3 drinking days</td>
<td>12</td>
<td>40–75</td>
<td>United States</td>
<td>Age, smoking (6 categories)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>M</td>
<td>193 combined</td>
<td>15–29.9 g</td>
<td>&lt;3 drinking days</td>
<td>≥3 drinking days</td>
<td></td>
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<tr>
<td>Study Reference</td>
<td>Study Type and Details</td>
<td>Sample Size</td>
<td>Criteria 1</td>
<td>Criteria 2</td>
<td>Age</td>
<td>Country</td>
<td>Additional Details</td>
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<tr>
<td>Murray et al. 48, 2002</td>
<td>Morbidity and mortality (physician visits, hospital stays and vital statistics files, ICD-9-CM codes 410–414)</td>
<td>M 139 combined</td>
<td>&lt;3 drinking days</td>
<td>≥3 drinking days</td>
<td>30–49.9 g</td>
<td>Canada</td>
<td>Age, total alcohol intake (g/day: 0.65–5.77, 5.78–18.1, &gt;18.1), education, marital status, smoking</td>
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<tr>
<td>Malyutina et al. 44, 2002</td>
<td>Mortality (death register, autopsy reports, MONICA register, ICD-9 codes 410–414)</td>
<td>M 59 combined</td>
<td>Any ≥8 drinks per occasion in the past year</td>
<td>None in the past year</td>
<td>80–120 g/drinking day</td>
<td>Russia</td>
<td>Age only</td>
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<tr>
<td>Malyutina et al. 44, 2002</td>
<td>Mortality (death register, autopsy reports, MONICA register, ICD-9 codes 410–414)</td>
<td>M 133/87</td>
<td>80–120 g/drinking day</td>
<td>&lt;80 g/drinking day</td>
<td>70/87</td>
<td>Russia</td>
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<tr>
<td>Kauhanen et al. 46, 1997</td>
<td>Fatal MI (WHO MONICA criteria (25))</td>
<td>M 6/22</td>
<td>≥6 drinks per occasion</td>
<td>&lt;6 drinks per occasion</td>
<td>5.6</td>
<td>Finland</td>
<td>Age, total alcohol consumption</td>
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<tr>
<td>Shaper et al. 50, 1987</td>
<td>Mortality (2 of 3 standard criteria: severe prolonged chest pain, electrocardiographic or enzyme changes, and mortality (death certificate))</td>
<td>M 24/20</td>
<td>&gt;6 drinks on weekends</td>
<td>3–5 drinks daily or almost daily</td>
<td>6.2</td>
<td>United Kingdom</td>
<td>Age, years of smoking, social class</td>
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<tr>
<td>Poikolainen 52, 1983</td>
<td>Mortality (death certificate, ICD-7)</td>
<td>M 27 combined</td>
<td>Once weekly</td>
<td>None in the past year</td>
<td>12</td>
<td>Finland</td>
<td>Age, marital status</td>
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<tr>
<td>Kozarevic et al. 39, 1982</td>
<td>Mortality (sudden and nonsudden CHD death, death certificate)</td>
<td>M 35/56</td>
<td>At least a month ago</td>
<td>Less than a month ago</td>
<td>7</td>
<td>Yugoslavia</td>
<td>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</td>
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</table>

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.

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

**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.
2.4.2 Meta-analysis

Prepooled and random-effects summary estimates are provided in Figure 2-2. 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 2-2) 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.

### 2.4.3 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).
2.5 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 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.

2.6 Acknowledgements

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Conflict of interest: none declared.
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Headings were included to reflect the structure of this dissertation.
3.1 Abstract

**Background:** The relationship between alcohol consumption and ischaemic heart disease (IHD) risk is complex and several issues remain unresolved because many studies used rather crude exposure measures often based on one or two questions. The objective of this study was to investigate the association between heavy drinking occasions and IHD mortality while controlling for average daily alcohol intake and separating former drinkers from lifetime abstainers.

**Methods:** Cox regression analyses were used with IHD mortality as the outcome in a sample of 9934 participants of the US National Alcohol Surveys conducted in 1984 and 1995.

**Results:** To the end of 2006, 326 deaths from IHD were recorded in the 11-22 year follow-up period. Any past heavy drinking occasions in former drinkers (hazard ratio [HR] = 2.06, 95% confidence interval [CI]: 1.10-3.85) compared with former drinkers without such drinking occasions, and any heavy drinking occasion in current drinkers at baseline (HR = 2.05, 95% CI: 1.03-3.98) compared to current drinkers with average daily intake of 1-2 drinks were associated with higher IHD mortality in men; and any heavy drinking occasions among drinkers of up to 1 drink average consumption in women with similar effect size. Confounding effects from age, race, education, employment, income, marital status, geographical region, depression score, survey period, or other drug use were small.

**Conclusions:** Among former and current drinkers, heavy drinking occasions should be taken into account when examining the complex association of alcohol consumption on IHD mortality risk.

Keywords: Ischaemic heart disease, alcohol consumption, binge drinking, heavy episodic drinking, cohort study, mortality
3.2 Introduction

The relationship between alcohol consumption and ischaemic heart disease remains controversial. Because evidence from long-term randomized trials is unavailable, one has to rely mostly on observational studies to investigate this relationship, of which many have shown some form of a beneficial association on heart disease (1-3). Generally, this relationship is described as a curvilinear (J-shape) with a relatively wide range of average daily alcohol intake associated with a potential cardioprotective effect without taking into account differential risks for former or heavy episodic drinkers (1). For different reasons - such as study design, exposure and covariate assessment, and statistical analysis - a potential cardioprotective association has been questioned many times (4-7). Furthermore, substantial heterogeneity across studies (e.g., for region, sex and mortality vs. morbidity) seen when examining average daily alcohol intake (1) suggests that important confounders or effect modifiers have not been well accounted for in prior studies. One possible explanation for differential risk (beyond sex and outcome) seems to be episodic heavy drinking occasions (8). In most of the larger cohorts, however, patterns of episodic heavy drinking were either not assessed or were very rare (9); furthermore, assessment of alcohol intake typically relied on few items, often only current usual quantity and frequency. In addition, most studies have not separated life-time abstainers from former drinkers, whose IHD mortality risk has been shown to be significantly higher in comparison to lifetime abstainers (10). We wanted to test the hypothesis that there would be an increased risk for IHD mortality from heavy alcohol consumption in former drinkers and current episodic heavy drinkers compared to respective drinking groups without such drinking behaviour after stratifying by sex in a follow-up study of a nationally representative US sample designed for assessment of alcohol intake patterns.
3.3 Methods

3.3.1 Subjects

Two cross-sectional waves (1984 and 1995) of the US National Alcohol Survey (NAS) were used as baseline data (11). Face-to-face interviews in the respondent’s home were used in both surveys. Response rates were 72% in 1984 and 77% in 1995. Participants were selected in a multi-stage area probability household sampling scheme, with Hispanics and African Americans over-sampled in both surveys. Data were collected by trained interviewers instructed to resolve inconsistencies during the interview. A total of 5177 participants 18 years or older were interviewed in their homes in 1984, and 5925 in 1995, resulting in a total sample of 10,146. Of these, 203 were excluded because of missing data on age (63), alcohol exposure (72), or race other than white, black, Hispanic, and Asian (70), resulting in an analysis sample of 9943. Participants were linked to mortality data from the National Death Index [NDI-Plus summaries (12)] to derive the time and cause of death using International Classification of Disease 9\textsuperscript{th} and 10\textsuperscript{th} Revision (ICD-9: 410-414; ICD-10: I20-I25) until Dec 31, 2006.

3.3.2 Exposure assessment

All questions on alcohol exposure were implemented identically in both surveys.

Drinking status

Participants who answered ‘I have never had wine/beer/whiskey or liquor’ to beverage-specific questions on how often they consumed alcohol were classified as lifetime abstainer. Those who reported consumption of ‘less than once a year’ for all types of beverages were classified as former drinker. Former drinking behaviour was further distinguished into those
who never consumed at least 5 drinks at one time and those who exceeded this limit based on a question about the largest number of drinks ever consumed. Analyzing this distinction between past drinking behaviour was not possible in women because of the small number of former drinkers with past heavy drinking occasions.

**Volume of alcohol consumption**

Usual frequency (no reference period given) of alcohol intake by beverage (wine/beer/liquor) was assessed with nine answer categories (from highest: three or more times a day, twice a day, once a day, nearly every day, 3 or 4 times per week, once or twice a week, two or three times a month, about once a month, less than once a month but at least once a year, less than once a year, never). In addition, answers to questions on the proportion of drinking as many as five to six drinks per occasion, and one to two drinks per occasion consumed recently by beverage type (answer options among drinkers of such beverage: nearly every time, more than half the time, less than half the time, once in a while) were used by a summation algorithm to derive total average daily alcohol intake (13;14). For the main analyses, the average daily number of drinks was converted into g/day and categorized into the following categories of total average daily alcohol volume with cut points reflecting occasional drinkers, those having one to two drinks, three to four drinks and five or more drinks (assuming 14 g of pure alcohol content per US standard drink (15)): 0, 0.1-2.49, 2.5-28, >28-56, and >56 g/day. In women, the highest category was taken as >14 g/day as the distribution of cases did not allow for a further distinction of categories.

**Current heavy drinking occasions**
We used the following indicators for current heavy drinking occasions in current drinkers at baseline: any positive answer to usual consumption of 5 or more drinks on one occasion by type of beverage (which also were used for the calculation of total average alcohol volume), or (because heavy drinking occasions involving more than one beverage could be missed) positive answers to specific questions on more than 12 and 8-11 drinks per drinking day in the past 12 months (any alcoholic beverage) (13;14).

3.3.3 Covariates

The list of potential confounders was restricted to the following because others, such as dietary intake other than alcohol, physical activity, or BMI were not assessed in the original surveys: race (White, Black, Hispanic, Asian), current smoking status (at least once every ≥2 months often vs not at all), marital status (yes vs no), education (less than high school, completed high school, some college, and completed college), employment status (full-time, retired, and others), income (<US$10 000, 10 000-<20 000, 20 000-<40 000, ≥40 000), born outside of the US among Hispanics, geographical region (Northeast, Midwest, Pacific, South, and Mountain), survey (1984 vs. 1995), depressive symptoms (CES-D ≥ 16) (16;17), and illegal drug use (at least once every ≥2 months often vs not at that level).

3.3.4 Outcome assessment

Out of a total of 1554 deaths from all causes, 326 deaths (3.3% of the total analysis sample, 20.9% of all recorded deaths in the analysis sample) due to IHD (ICD-9: 410-414; ICD-10: I20-I25) were recorded until the end of 2006.
3.3.5 Statistical analyses

Time in number of days from the date of the interview to either IHD death or December 31, 2006 was used in Cox proportional hazard regression analyses. All analyses were conducted separately by sex and adjusted for age (years). Proportional hazards assumptions were tested using Schoenfeld residuals. Age was the only variable violating this assumption and therefore an interaction term between age and natural log-time was included in all models. First, the association between total average daily alcohol consumption at baseline and IHD mortality with current non-drinkers as the reference group was estimated. Then, current non-drinkers were divided into lifetime abstainer and former drinker with lifetime abstention as the reference group. Successively, indicator variables for former drinker with any heavy drinking occasion in the past (among men only), and current drinkers of 1 or 2 drinks average daily consumption with any episodic heavy drinking occasion in the year before the baseline interview were added to this model. Sensitivity analyses were conducted excluding deaths in the first 2 years of follow-up to avoid reverse causality problems when already diseased subjects had changed their consumption prior to baseline, and IHD deaths beyond 75 years of age at the time of death because of potentially compromised accuracy of the cause of death ascertainment (18). We further tested the heavy drinking contrasts in subgroups defined by age, smoking status, other drug use, survey, and depressive symptoms where this was possible based on the number of cases. Statistical analyses were conducted in SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).
3.4 Results

Mean (SD) follow-up time was 15.1 (6.1) years and mean age at the time of IHD death was 71.1 (13.2) years in men, and 16.0 (6.1) years of follow-up, 75.1 (14.3) years of age in women. Among men, 29.6% were non-drinkers at baseline, of which slightly more than half were former drinkers; 65.1% (967) of current drinkers with 2.5-28 g/day average daily intake were classified as drinkers with episodic heavy drinking occasions (Table 3-1). Among women 37.3% (1034) of all non-drinkers at baseline were former drinkers and less than 10% (532) of women in the sample reported average daily alcohol consumption beyond 14 g/day (Table 3-2). Although the distributions of several potential confounders were quite different across drinking groups, the effect estimates from regression analyses were not influenced by these differences.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lifetime abstainer</th>
<th>Former drinker</th>
<th>Average daily alcohol intake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>0.1-2.49 g/day</td>
</tr>
<tr>
<td>Participants</td>
<td>640 (15.1)</td>
<td>1485 (35.1)</td>
<td>370 (8.8)</td>
</tr>
<tr>
<td>IHD deaths</td>
<td>640 (15.1)</td>
<td>29</td>
<td>38</td>
</tr>
<tr>
<td>Any heavy drinking occasions</td>
<td>617 (14.6)</td>
<td>201 (25.7)</td>
<td>331 (89.5)</td>
</tr>
<tr>
<td>past year (yes)</td>
<td>640 (15.1)</td>
<td>41.5 (16.4)</td>
<td>39.1 (15.0)</td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td>48.0 (18.5)</td>
<td>189 (24.2)</td>
<td>144 (18.5)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>62 (10.0)</td>
<td>130 (16.6)</td>
<td>508 (34.2)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>123 (19.2)</td>
<td>281 (18.9)</td>
<td>109 (29.5)</td>
</tr>
<tr>
<td>Black</td>
<td>177 (27.7)</td>
<td>434 (29.2)</td>
<td>117 (31.6)</td>
</tr>
<tr>
<td>Asian</td>
<td>201 (30.5)</td>
<td>262 (17.6)</td>
<td>95 (25.7)</td>
</tr>
<tr>
<td>Education</td>
<td>109 (17.9)</td>
<td>419 (28.3)</td>
<td>126 (38.0)</td>
</tr>
<tr>
<td>Less than high school</td>
<td>114 (17.9)</td>
<td>109 (29.5)</td>
<td>126 (38.0)</td>
</tr>
<tr>
<td>High school completed</td>
<td>131 (20.5)</td>
<td>152 (19.5)</td>
<td>117 (31.6)</td>
</tr>
<tr>
<td>Some college</td>
<td>48 (8.8)</td>
<td>144 (18.5)</td>
<td>61 (16.5)</td>
</tr>
<tr>
<td>College completed</td>
<td>65 (10.2)</td>
<td>269 (18.1)</td>
<td>54 (16.3)</td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Among women, 37.3% (1034) of all nondrinkers at baseline were former drinkers and <10% (532) of the women in the sample reported average daily alcohol consumption beyond 14 g/day (Table 3-2).

### Table 3-2. Sample characteristics at baseline by average daily total alcohol consumption in women (n = 5690)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lifetime abstainer</th>
<th>Former drinker</th>
<th>Average daily alcohol intake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>0.1-2.49 g/day</td>
</tr>
<tr>
<td>Participants</td>
<td>1740 (30.6)</td>
<td>1034 (18.2)</td>
<td>1517 (26.7)</td>
</tr>
<tr>
<td>IHD deaths</td>
<td>78 (4.5)</td>
<td>30 (2.9)</td>
<td>38 (2.5)</td>
</tr>
<tr>
<td>Any heavy drinking occasions past year (yes)</td>
<td>208 (13.7)</td>
<td>349 (40.3)</td>
<td>392 (73.7)</td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td>47.9 (19.6)</td>
<td>44.9 (18.3)</td>
<td>40.8 (16.4)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>200 (11.5)</td>
<td>174 (16.8)</td>
<td>314 (20.7)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>664 (38.2)</td>
<td>326 (31.5)</td>
<td>427 (28.1)</td>
</tr>
<tr>
<td>Black</td>
<td>560 (32.2)</td>
<td>369 (35.7)</td>
<td>577 (38.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>316 (18.2)</td>
<td>165 (16.0)</td>
<td>199 (13.1)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>906 (52.2)</td>
<td>402 (39.0)</td>
<td>396 (26.1)</td>
</tr>
<tr>
<td>High school completed</td>
<td>493 (28.4)</td>
<td>354 (34.3)</td>
<td>541 (35.7)</td>
</tr>
<tr>
<td>Some college</td>
<td>241 (13.9)</td>
<td>182 (17.6)</td>
<td>355 (23.4)</td>
</tr>
</tbody>
</table>

CES-D, Center for Epidemiologic Studies Depression Scale.
Table 3-3 shows the relationship between average per day alcohol consumption and IHD mortality. Regarding men, with non-drinkers as the reference group, a somewhat U-shaped curve emerged (Model 1). Having lifetime abstainer as the reference group (Model 2, fully-adjusted), the HR for former drinking was 1.26 (95% CI: 0.78-2.02) and the curve shifted upwards, bringing point estimates for average daily alcohol intake categories closer to 1 for average intake up to 56 g/day resulting in a J-shaped curve. In women, former drinking showed a small decreased risk of IHD mortality. Confidence intervals were generally wide and included 1 for all estimates in Table 3-3.

Among men, adding contrasts depicting any former heavy drinking occasions among former drinkers and episodic heavy drinking occasions in current drinkers of 2.5-28 g/day average daily intake showed substantial risk increases with similar effect sizes (HR=2.06 [95% CI: 1.10-3.85], and 2.02 [1.03-3.98], respectively) (Table 3-4).
<table>
<thead>
<tr>
<th>Variable</th>
<th>Number</th>
<th>IHD Deaths, No.</th>
<th>Age-adjusted Hazard ratio (95% CI)</th>
<th>Model 1</th>
<th>Fully adjusted Hazard ratio (95% CI)</th>
<th>Model 2</th>
<th>Fully adjusted Hazard ratio (95% CI)</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>P value</td>
<td></td>
<td>P value</td>
<td></td>
<td>P value</td>
<td></td>
</tr>
<tr>
<td>Men (n = 4226)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-drinkers at baseline</td>
<td>1257</td>
<td>76</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lifetime abstainer</td>
<td>617</td>
<td>34</td>
<td>-</td>
<td>-</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former drinker</td>
<td>640</td>
<td>42</td>
<td>-</td>
<td>-</td>
<td>1.28 (0.81-2.03)</td>
<td>0.29</td>
<td>1.26 (0.78-2.02)</td>
<td>0.34</td>
</tr>
<tr>
<td>Current drinker at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.01-2.49 g/day</td>
<td>781</td>
<td>29</td>
<td>0.92 (0.59-1.42)</td>
<td>0.70</td>
<td>0.91 (0.58-1.43)</td>
<td>0.68</td>
<td>1.05 (0.63-1.75)</td>
<td>0.86</td>
</tr>
<tr>
<td>2.5-28 g/day</td>
<td>1485</td>
<td>38</td>
<td>0.75 (0.50-1.12)</td>
<td>0.16</td>
<td>0.78 (0.51-1.18)</td>
<td>0.24</td>
<td>0.85 (0.53-1.39)</td>
<td>0.53</td>
</tr>
<tr>
<td>&gt;28-56 g/day</td>
<td>370</td>
<td>6</td>
<td>0.45 (0.20-1.05)</td>
<td>0.064</td>
<td>0.47 (0.20-1.10)</td>
<td>0.080</td>
<td>0.52 (0.22-1.25)</td>
<td>0.14</td>
</tr>
<tr>
<td>&gt;56 g/day</td>
<td>333</td>
<td>11</td>
<td>1.05 (0.53-2.07)</td>
<td>0.89</td>
<td>1.08 (0.54-2.18)</td>
<td>0.83</td>
<td>1.20 (0.58-2.49)</td>
<td>0.63</td>
</tr>
<tr>
<td>Women (n = 5690)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-drinkers at baseline</td>
<td>2774</td>
<td>108</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lifetime abstainer</td>
<td>1740</td>
<td>78</td>
<td>-</td>
<td>-</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former drinker</td>
<td>1034</td>
<td>30</td>
<td>-</td>
<td>-</td>
<td>0.82 (0.54-1.25)</td>
<td>0.35</td>
<td>0.87 (0.56-1.35)</td>
<td>0.56</td>
</tr>
<tr>
<td>Current drinker at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.01-2.5 g/day</td>
<td>1517</td>
<td>38</td>
<td>1.03 (0.71-1.50)</td>
<td>0.90</td>
<td>1.13 (0.76-1.69)</td>
<td>0.54</td>
<td>0.97 (0.65-1.43)</td>
<td>0.85</td>
</tr>
<tr>
<td>2.5-14 g/day</td>
<td>867</td>
<td>12</td>
<td>0.76 (0.41-1.39)</td>
<td>0.36</td>
<td>0.87 (0.46-1.63)</td>
<td>0.65</td>
<td>0.71 (0.38-1.32)</td>
<td>0.27</td>
</tr>
<tr>
<td>&gt;14 g/day</td>
<td>532</td>
<td>8</td>
<td>0.69 (0.34-1.43)</td>
<td>0.32</td>
<td>0.82 (0.39-1.75)</td>
<td>0.61</td>
<td>0.64 (0.31-1.34)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Note: Fully adjusted model includes: age, smoking status, race, education, employment status, marital status, income, survey, region, depression symptoms (CES-D ≥16), born outside the US (among Hispanics only), other drug use.
Table 3-4. IHD mortality after 11-22 years of follow-up for heavy drinking contrasts at baseline (1984 and 1995) (n = 9934)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number</th>
<th>IHD Deaths, No.</th>
<th>Men Age-adjusted Hazard ratio (95% CI)</th>
<th>P value</th>
<th>Fully adjusted Hazard ratio (95% CI)</th>
<th>P value</th>
<th>Women Age-adjusted Hazard ratio (95% CI)</th>
<th>P value</th>
<th>Fully adjusted Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Former drinker without heavy drinking occasions</td>
<td>317</td>
<td>18</td>
<td>1 (reference)</td>
<td></td>
<td>1 (reference)</td>
<td></td>
<td>859</td>
<td>29</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Former drinker with any past heavy drinking occasion</td>
<td>323</td>
<td>24</td>
<td>2.06 (1.12-3.82)</td>
<td>0.021</td>
<td>2.06 (1.10-3.85)</td>
<td>0.024</td>
<td>175</td>
<td>1</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Current drinker without heavy drinking occasions</td>
<td>509</td>
<td>17</td>
<td>1 (reference)</td>
<td></td>
<td>1 (reference)</td>
<td></td>
<td>518</td>
<td>7</td>
<td>1 (reference)</td>
<td></td>
</tr>
<tr>
<td>Current drinker with any current heavy drinking occasions</td>
<td>967</td>
<td>21</td>
<td>2.05 (1.06-3.96)</td>
<td>0.033</td>
<td>2.02 (1.03-3.98)</td>
<td>0.041</td>
<td>349</td>
<td>5</td>
<td>2.10 (0.66-6.65)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Note: All models were adjusted for alcohol categories as displayed in Model 2 in Table 3-3; Fully-adjusted models further include: smoking status, race, education, employment status, marital status, income, survey, region, depression symptoms (CES-D ≥16), born outside the US (among Hispanics only), other drug use.

a Within average daily alcohol consumption of 2.5-28 g/day in men, 2.5-14 g/day in women.
Indeed, of all covariates included in the regression models, these two heavy drinking contrasts were most strongly associated with IHD mortality risk (other than age), whether indicated by $P$-value or effect size. With lifetime abstainer as the reference group, the corresponding risk for former drinkers reporting any past heavy drinking occasions in men was HR = 1.83 (95% CI: 1.06-3.17), and HR = 1.27 (95% CI: 0.69-2.34) for current drinkers with episodic heavy drinking occasions within 2.5-28 g/day average alcohol intake. The association of any current heavy drinking in women with 2.5-14 g/day average intake showed similar effect size compared with men. Additional adjustment for covariates did not substantially change any of the alcohol estimates in the analysis. Using the fully-adjusted models, sensitivity analyses did not show substantial changes. Separate subgroup analyses revealed that the associations for former or current heavy drinking were very similar in those who did not use other drugs. However, the association of former heavy drinking was restricted to older men (> 65 years), and the association of current heavy drinking episodes to those between 40-65 years. In each age group, the respective associations were similar when the sample was simultaneously restricted to non-smokers and men with CES-D < 16. The association of current heavy drinking episodes was also similar across surveys (1984 and 1995). Former heavy drinking occasions showed stronger associations in the 1984 sample, and no association in the 1995 sample. Such subgroup analyses were not possible in women because of the small number of cases in each cell.

### 3.5 Discussion

This study, using more detailed measurement of exposure than previous studies, showed the importance of distinguishing between drinking patterns in both former drinkers and current drinkers with low average intake (on average 2 drinks per day or less, usually thought to be
beneficial for heart disease) in men. An almost identical association was found in women for current drinkers up to 1 drink per day. However, owing to low power due to the small number of IHD deaths in drinking categories, confidence intervals were wide, particularly among women. Nevertheless, the association of former drinking and current heavy drinking was consistent across sexes and in several sensitivity analyses and subgroup-analyses. Although confounding was small in all models, particular age seems to be a strong influence on the association of alcohol consumption on IHD mortality risk in general, and particularly for heavy drinking occasions. Given these findings, current average daily alcohol consumption alone does not seem to adequately capture the alcohol-IHD risk relationship, and particularly for men the deleterious role of any heavy drinking in former drinkers as well as in current drinkers of 1-2 drinks on average was apparent.

3.5.1 Limitations

Although assessment of alcohol intake in surveys seems to be reasonably valid (14;19), it generally underestimates total per capita alcohol consumption in a population compared with sales statistics despite a correlation between the two over time (20;21). However, we used several items to assess heavy alcohol consumption in the sample, and used multiple beverage specific items to derive total daily average alcohol intake. Both these factors generally result in higher estimated total alcohol consumption in population surveys (14;22-29). Importantly, we used multiple items for identifying drinkers with heavy drinking occasions at baseline and thus have confidence that we have separated those with potentially deleterious patterns from drinkers with no such drinking behaviour. However, as in many other studies, we relied on baseline assessment of alcohol exposure and; although past drinking behaviour was taken into account in a crude measure (5 or more drinks ever in former drinker), alcohol
consumption over the life course might have changed during follow-up or prior to baseline more than we were able to capture with our measurements. More detailed assessment of frequency of heavy drinking occasions over the life course certainly would help to shed light into the alcohol heart relationship given that both moderate drinking and heavy drinking have been shown to vary over time (30). Furthermore, even lifetime abstainer can be misclassified with a one-time only measurement (31;32). Although accuracy of cause of death ascertainment is diminished at higher age at time of death, excluding deaths occurring beyond 75 years of age revealed similar effects to the main analysis. Confounding was small in all models and indicators for heavy drinking episodes among both former and current mid-volume (1-2 drinks/day) drinkers showed substantial effect sizes; however, our list of potential confounders was not complete and we cannot exclude the possibility that these unmeasured confounders, such as medical history, dietary factors other than alcohol, or physical activity, explain the results of this study. Although many confidence intervals included 1, small sample size might have precluded us from detecting significant effects in some drinking groups, rather than the effect estimates not being important. This is supported by the sensitivity and subgroup analyses. Lastly, using observational data we can only examine associations and so avoid statements on causality of effects.

3.5.2 Implications

A recent meta-analysis showed a significantly elevated pooled relative risk for IHD death in former drinkers compared to long-term abstainers in both sexes without taking into account specific former drinking behaviour (10). Few studies have addressed former drinking behaviour and these were mostly based on former average consumption (33-36). The present study indicates that it is important to not only separate former drinkers from lifetime
abstainer, but also distinguish between former drinkers who do and do not have past heavy drinking behaviour.

A recent meta-analysis showed a relative risk of 1.45 (95% CI: 1.24-1.73) for drinkers with usual heavy drinking occasions compared to current drinkers without usual episodic heavy drinking, using relatively crude measures of heavy drinking identified by usual quantity-frequency measurements without the detail in exposure measurement used in the present study. A recent study comparing the risk of myocardial infarction and coronary deaths from binge drinking in relation to regular drinkers in France and Northern Ireland (37) showed similar effect sizes with an RR = 1.81, 95% CI: 1.05-3.11 for binge drinking in comparison to regular, non-binge drinkers in Northern Ireland, similar to our findings. Our results not only confirm this increased risk, but also suggest that the difference in risk might be strongest in low consumption of up to and including 2 drinks per day on average. This suggests that heavy drinking occasions should be avoided altogether and when engaged in, may not confer any cardioprotective effect even at low levels of average consumption (HR compared to lifetime abstainer = 1.17, 95% CI: 0.65-2.08). High and rising prevalence of binge drinking in many countries give reason for public health concern (38;39). Possible adverse effects of heavy drinking occasions on heart disease include increased blood pressure, fibrinolytic factors and ventricular arrhythmia after cessation of drinking (40), in contrast to a cardioprotective association of regular moderate alcohol consumption through an increase in high-density lipoproteins, inhibition of platelet activation, and fibrinolytic factors (41). A comprehensive review concluded that low-density lipoproteins are increased
by heavy drinking episodes, and no increase in high-density lipoprotein levels (42), although the evidence is inconsistent (43).

Nevertheless, we cannot comment on the influence of episodic heavy drinking occasions as we defined them beyond 28 g/day average daily alcohol intake in men and 14 g/day in women simply because there were not enough participants who exhibited average daily alcohol consumption of 3-4 drinks per day without any heavy drinking occasions. A potential cardioprotective association seemed to be evident up to 72 g/day average alcohol intake in the most recent meta-analysis (1), suggesting a potentially beneficial association in drinkers beyond 1-2 drinks average intake. It is possible that the beneficial effect on IHD is strongest at higher intake than two drinks per day on average even when heavy drinking episodes were present. However, this remains speculative because there is little data with which to investigate episodic heavy drinking in this range of average intake. Furthermore, for any particular individual, the alcohol-IHD relationship cannot be seen in isolation from other disease outcomes because even at low levels of alcohol intake the effect on many other disease outcomes is detrimental (44;45), and 3-4 drinks on average is not a safe consumption level from a clinical or public health perspective as it has been shown to be detrimentally associated with many other disease outcomes (46).

3.6 Conclusions

This study confirms earlier research and gives further weight to arguments that the relationship between alcohol consumption and IHD mortality is quite complex and even non-linear modeling of only current average volume is insufficient to reflect this complexity. Moreover, for investigating IHD mortality risk associations, it confirmed the importance of
separating lifetime abstainer, former drinkers and the latter’s past drinking behaviour, in addition to heavy drinking occasions among low to moderate drinkers. It seems that heavy drinking occasions are an important component in determining IHD mortality risk in past or present alcohol consumers.

3.7 Funding


The H. David Archibald Award, the Inge and Ralf Hoffmann Graduate Scholarship, and the Heart & Stroke Foundation of Ontario Fellowship (all from the Faculty of Medicine, University of Toronto, Toronto, Canada) (to M.R.).

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Conflict of interest: None declared
3.9 References


Chapter 4: Life Course Frequency of Heavy Drinking Occasions and Heart Disease Mortality After 11 Year Follow-Up of The 1995 US National Alcohol Survey
4.1 Abstract

**Background:** Most of the research on alcohol consumption and risk of heart disease is based on current average alcohol intake, often incorporating only one or two questions. We identified groups of heavy drinking behaviour over the life course, and determined their risk of mortality from heart disease in a US national sample.

**Methods:** Growth mixture modeling was used to identify latent classes of heavy drinking frequency over the life course, and Cox regression analyses were used to relate these classes to heart disease mortality in 971 male participants 41 years or older from the US National Alcohol Survey conducted in 1995.

**Results:** At the end of 2006, 63 deaths from heart disease were recorded in the 11 year follow-up period. Four classes of heavy drinking trajectories were identified. One class showed relatively low frequency of heavy drinking over the life course, another showed an early rise followed by a rapid decline, and two classes showed substantial increases in heavy drinking frequency over time. Lifetime abstainers were at highest risk of heart disease mortality, while participants with low frequency of heavy drinking throughout were associated with the lowest risk. Confounding effects from age, race, education, employment, marital status, geographical region, depression score, or other drug use, were small.

**Conclusions:** Distinct trajectories of heavy drinking over the life course were identified. There was no evidence for an increased risk of heart disease mortality in any drinking group. A much larger sample size is required to estimate the risk of heart disease in drinking groups exhibiting high prevalence of heavy drinking days over the life course.
4.2 Introduction

Despite being one of the most researched associations in alcohol epidemiology, many questions remain about the relationship between alcohol consumption and heart disease. Several meta-analyses have found either L- or J-shaped curves for average daily alcohol consumption in both men and women, although the curves for women were generally characterized by a lower nadir and upturn at lower levels of average alcohol consumption (9, 11, 40). Epidemiological evidence is supported by experimental evidence for a favourable association of regular low to moderate alcohol consumption on high density lipoproteins, inhibition of platelet aggregation, and reduced fibrinogen levels (5, 36). Aside from average daily alcohol intake, several dimensions of alcohol exposure and effect modifiers that play a role in determining the risk of heart disease associated with alcohol consumption have been identified. For example, although average volume of drinking has been the focus of research to date (14, 34), the potential importance of drinking patterns has long been recognized (41) and recently reinforced (1). Recent individual studies (37, 43) and meta-analyses (3, 38) have shown evidence of the impact of heavy drinking occasions over and above average daily alcohol consumption on heart disease and all-cause mortality (26). Moreover, many studies have not separated lifetime abstainers from former drinkers. That being said, former drinkers might have quit for health reasons and therefore might have a higher baseline risk than true lifetime abstainers, which might lead to artificially raised risk when current abstainers are used as the comparison group (15, 46). From a life course perspective, former drinkers should be classified as a form of drinker rather than abstainer. In addition to the problem of lifetime abstention and current abstention, many drinkers also change their consumption over time, particularly with respect to heavy drinking (24). However, the vast
majority of epidemiological studies have had to rely on a one time baseline measurement only, thus not accounting for change in alcohol intake over time. There is limited knowledge on change of alcohol intake over the lifetime and virtually no research on heavy drinking days (5 or more drinks per day) over the lifetime with regard to heart disease risk from cohort studies (22). Some studies used lifetime drinking history for retrospective assessment (12, 16) or updated alcohol intake over the time of follow-up in relation to disease outcomes (10, 49), all studies used average daily alcohol intake over the life course. Some were conducted in prolonged heavy drinkers recruited from outpatient clinics for alcoholics (23), and in some cases, measured self-reported heart disease prevalence as the outcome (25). Without taking into account heavy drinking episodes, Friesema et al. (2008) examined variations of average daily alcohol intake on cardiovascular events, including stroke and heart failure, and reported a strong association with current drinking, but no significant association with lifetime measures of average alcohol intake (16). Fan et al. (2008) identified two trajectories by retrospective measurement of average volume in a cross-sectional study: one with an early peak, and one with more stable consumption with a peak around the 4th and 5th lifetime decade in a US sample (12). The early peak trajectory was associated with several biomarkers and risk factors for heart disease, such as higher odds of metabolic syndrome, low high-density lipoproteins, and abdominal obesity or being overweight at the baseline assessment. However, no study examined histories of heavy drinking episodes on heart disease mortality. Our objective was to investigate how the frequency of heavy drinking days changes over time and how different patterns of change influence heart disease mortality risk. We used data from the US National Alcohol Survey conducted in 1995, which was designed to assess alcohol consumption and includes
questions on frequency of heavy drinking occasions from drinkers’ teenage years through their forties. Participants were followed-up for heart disease mortality over an 11 year period.

4.3 Material and Methods

4.3.1 Participants

Male participants in the 1995 wave of the US National Alcohol Survey (NAS), conducted from April 1995 to April 1996 by the Temple University Institute for Survey Research (Philadelphia, Pennsylvania) for the Alcohol Research Group at the Public Health Institute (Emeryville, California), were used as baseline data (20). Participants were selected in a multi-stage area probability household sampling scheme, with oversampling of Hispanics and African Americans. Face-to-face interviews were conducted in the respondent’s home with an overall response rate of 77%. Data were collected by trained interviewers instructed to resolve inconsistencies during the interview. Out of a total of n = 2,220 male participants 18 years or older, n = 1,044 were 41 or older and provided information on life course heavy drinking frequency from their teens to forties. A total of 73 participants were excluded because of missing data: n=10 with missing data on race, n=7 with missing baseline alcohol exposure, and n=56 with two or more missing values on the four life course measurements. The final sample for analysis was n = 971 male participants.

4.3.2 Exposure assessment

Drinking status

Participants who answered ‘I have never had wine/beer/whiskey or liquor’ to beverage-specific questions on how often they consumed alcohol were classified as lifetime abstainers. Those who reported consumption of ‘less than once a year’ for all types of beverages (i.e.,
those who did not drink at least 1 drink in the 12 months prior to the baseline interview), were classified as former drinkers. Former drinking behavior was further distinguished into those who never consumed at least 5 drinks at one time, and those who exceeded this limit based on a question about the largest number of drinks ever consumed.

**Volume of alcohol consumption**

Among current drinkers at baseline in 1995, current alcohol consumption was assessed using the Graduated-Frequency approach (26-28). This includes a series of questions about drinking days with 12 drinks or more, 8-11, 5-7, 3-4, and 1-2 drinks (any type of alcoholic beverage) in the past 12 months. Answers to these questions were used to calculate average daily alcohol intake in g/day, assuming 14 grams of pure alcohol per drink.

**Frequency of heavy drinking occasions from teens to forties**

The frequency of heavy drinking days (5 or more drinks/day) during teen years, 20s, 30s, and 40s was retrospectively assessed with nine answer categories ranging from ‘never in the past year’ to ‘every day or nearly every day’ among those participants (former or current drinkers) who answered that they had ever drank 5 or more drinks per day. Category midpoints were used to calculate the number of drinking days with 5 or more drinks per day in the past year for each assessment time point.

**4.3.3 Covariates**

The list of potential confounders was restricted to the following because others, such as dietary intake other than alcohol, physical activity, or body mass index were not assessed in the original surveys: race/ethnicity (White vs. other), current smoking status (at least once
every two months or more often vs. not at all), marital status (yes vs. no), education (completed college vs. other), employment status (full-time vs. other), geographical region (South vs. other), depressive symptoms (CES-D ≥ 16) (29, 30), and illegal drug use (at least once every two months or more often vs. not at that level).

4.3.4 Outcome assessment

Participants were linked to mortality data from the National Death Index [NDI-Plus summaries (31)] to derive the time and cause of death using International Classification of Disease (ICD) 9th and 10th Revision until Dec 31, 2006. First and last name, middle initial, gender, race, state of birth and residence, marital status, and year of birth were used to match survey participants to death certificates records in the National Death Index, from which cause and date of death were obtained. Out of a total of 204 deaths (21.0%) from all causes, 63 deaths (6.5%) from heart disease (ICD-9: 390-398, 402, 404, 410-429; ICD-10: I00-I09, I11, I13, I20-I51) were recorded between the day of the baseline interview in 1995 and the end of 2006.

4.3.5 Statistical analyses

Growth mixture modeling (GMM) using maximum likelihood optimization was used to identify unobserved latent classes of frequency of heavy drinking occasions over the life course (all assessed retrospectively at baseline in 1995), allowing for intra-class variability. Posterior probabilities of group membership determined the group to which an individual participant was assigned. Entropy (32), the Bayesian information criterion (BIC) (33), and Akaike’s information criterion (AIC) (34) were used to assess model fit. Model fit indices, parsimony and class interpretability drove the final decision on the number of classes (35-
Time in number of days from the date of the baseline interview to either heart disease death or December 31, 2006 was used in Cox proportional hazard regression analyses. Deaths from causes other than heart disease were censored at the time of death. Proportional hazards assumptions were tested using Schoenfeld residuals. Confounding effects from available covariates were tested one by one in separate Cox regression models containing all drinking groups and age. Confounding was assumed to be present when hazard ratios for any alcohol groups changed more than 10%. Bootstrap sampling based on n = 5,000 samples was applied to evaluate the validity of confidence intervals from Cox regression models. Statistical analyses were conducted in Mplus version 6.11 and SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

4.4 Results

Mean follow-up time in years (SD) was 10.2 (2.7) for all participants and 5.3 (3.4) among heart disease mortality cases. Those participants who reported that they had consumed 5 or more drinks in one day at least once in their life were used to identify latent classes of heavy drinking frequency from their teens to forties in a growth mixture model. Intercepts of heavy drinking frequency variables were fixed at zero and their residual variances were allowed to differ across time. Residual variances of these variables were not correlated. The covariance of the residuals of the random-effects growth factors (intercept, slope, and quadratic slope) were estimated because their only relationship is with the heavy drinking frequency variables. Intercepts of these growth factors were freely estimated, but residual covariances were held equal across classes because of convergence problems. Solutions for 2, 3, or 4 classes showed good model fit in terms of entropy (Table 4-1). The 4 class solution had the lowest AIC and BIC compared with the 2 and 3 class solutions and showed clear distinction
of drinking trajectories as defined by entropy. Figure 4-1 shows the estimated means of the 4 class solution from participants’ teenage years to their forties. The majority of drinkers who had at least one heavy drinking episode in this time of their life were in class 1 with a relatively low and slightly declining frequency of heavy drinking days throughout this time frame. Class 2 showed a steep rise in frequency and then a strong decline from their thirties to forties. Class 3 and 4 showed a steady increase in heavy drinking frequency which reached almost daily heavy drinking in their forties in class 4.

Table 4-1. Model Fit Indices for Life Course Heavy Drinking Frequency Trajectories (n = 677)

<table>
<thead>
<tr>
<th>Model fit index</th>
<th>Number of classes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td>AIC</td>
<td>27814</td>
</tr>
<tr>
<td>BIC</td>
<td>27891</td>
</tr>
<tr>
<td>Entropy</td>
<td>0.99</td>
</tr>
</tbody>
</table>

AIC, Akaike’s information criterion, BIC, Bayesian information criterion
Figure 4-1. **Heavy drinking trajectories over the life course** *(n = 677 ever 5 or more drinkers)*. Class 1, low throughout *(n = 541)*; class 2, increasing then decline *(n = 40)*; class 3, steady increasing *(n = 52)*; class 4, steep increasing *(n = 44)*.

Overall, 69% of the sample (classes 1-4) had at least one heavy drinking episode in their lifetime, as reported at the time of the baseline interview in 1995 (Table 4-2). All of the participants who reported never having had 5 or more drinks per day from their teens to forties also reported no heavy drinking episodes in the year before the baseline survey in 1995. Former drinkers were more prevalent among classes with increasing frequency of heavy drinking up to the forties, but had little influence on the relationship between lifetime abstainers and those drinkers who had a relatively low frequency of heavy drinking days up to their forties. Smoking and other drug use was most prevalent in classes 2-4, which had the highest prevalence of heavy drinking days from their teens to forties. The proportion of
participants from the South or those who were married at the time of the baseline interview was highest in lifetime abstainers. Mean age was lowest in class 2, and highest among drinkers who never had a heavy drinking episode.

### Table 4-2. Sample Characteristics at Baseline (1995) by Classes of Heavy Drinking Frequency From Teens to Forties in Men (n = 971)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lifetime abstainer</th>
<th>Never 5 or more drinks per day</th>
<th>Class 1 Steady low</th>
<th>Class 2 Rise then fall</th>
<th>Class 3 Steady increase</th>
<th>Class 4 Steep increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%</td>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Participants</td>
<td>179 (18.4)</td>
<td>115 (11.8)</td>
<td>541 (55.7)</td>
<td>40 (4.1)</td>
<td>52 (5.4)</td>
<td>44 (4.5)</td>
</tr>
<tr>
<td>Heart disease deaths</td>
<td>20</td>
<td>14</td>
<td>22</td>
<td>48.2 (6.1)</td>
<td>56.4 (12.3)</td>
<td>66.5 (12.8)</td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td>60 (33.5)</td>
<td>43 (37.4)</td>
<td>226 (41.8)</td>
<td>7 (17.5)</td>
<td>23 (44.2)</td>
<td>14 (31.8)</td>
</tr>
<tr>
<td>Average alcohol volumea g/day, mean (SD)</td>
<td>NA</td>
<td>2.2 (4.3)</td>
<td>9.3 (13.5)</td>
<td>17.8 (33.5)</td>
<td>47.8 (36.4)</td>
<td>66.5 (54.7)</td>
</tr>
<tr>
<td>Former drinkerc</td>
<td></td>
<td>83 (72.2)</td>
<td>88 (16.3)</td>
<td>12 (30.0)</td>
<td>10 (19.2)</td>
<td>14 (31.8)</td>
</tr>
<tr>
<td>Race</td>
<td>60 (33.5)</td>
<td>43 (37.4)</td>
<td>226 (41.8)</td>
<td>7 (17.5)</td>
<td>23 (44.2)</td>
<td>14 (31.8)</td>
</tr>
<tr>
<td>Education</td>
<td>17 (9.5)</td>
<td>12 (10.4)</td>
<td>114 (21.1)</td>
<td>4 (10.0)</td>
<td>5 (9.6)</td>
<td>3 (6.8)</td>
</tr>
<tr>
<td>Employment status</td>
<td>72 (40.2)</td>
<td>39 (33.9)</td>
<td>318 (58.8)</td>
<td>22 (55.0)</td>
<td>19 (36.5)</td>
<td>16 (36.4)</td>
</tr>
<tr>
<td>Full-time</td>
<td>120 (67.0)</td>
<td>72 (62.6)</td>
<td>319 (59.0)</td>
<td>22 (55.0)</td>
<td>26 (50.0)</td>
<td>24 (54.5)</td>
</tr>
<tr>
<td>Marital status</td>
<td>103 (57.5)</td>
<td>56 (48.7)</td>
<td>211 (39.0)</td>
<td>16 (40.0)</td>
<td>25 (48.1)</td>
<td>17 (38.6)</td>
</tr>
<tr>
<td>South</td>
<td>36 (20.1)</td>
<td>26 (22.6)</td>
<td>193 (35.7)</td>
<td>25 (62.5)</td>
<td>27 (51.9)</td>
<td>25 (56.8)</td>
</tr>
<tr>
<td>Smoking status</td>
<td>103 (57.5)</td>
<td>56 (48.7)</td>
<td>211 (39.0)</td>
<td>16 (40.0)</td>
<td>25 (48.1)</td>
<td>17 (38.6)</td>
</tr>
<tr>
<td>Smoker</td>
<td>27 (15.1)</td>
<td>16 (13.9)</td>
<td>46 (8.5)</td>
<td>6 (15.0)</td>
<td>10 (19.2)</td>
<td>12 (27.3)</td>
</tr>
<tr>
<td>Depression CES-D≥16 (yes)</td>
<td>18 (10.1)</td>
<td>11 (9.6)</td>
<td>101 (18.7)</td>
<td>12 (30.0)</td>
<td>14 (26.9)</td>
<td>11 (25.0)</td>
</tr>
</tbody>
</table>

a Among current drinkers at baseline in 1995
b CES-D, Center for Epidemiologic Studies Depression Scale
c At baseline interview in 1995
NA, not applicable

When the drinking groups identified in the growth mixture model were related to heart disease mortality over the 11 year follow-up period, all drinking groups showed reduced risk of dying from heart disease compared with lifetime abstainers (Table 4-3). The risk reduction was strongest within the drinking group having reported a relatively low frequency
of heavy drinking over the life course (multivariate HR = 0.54, 95% CI 0.29-1.00). There was little bias as determined by bootstrap confidence intervals (multivariate HR = 0.54, 95% CI: 0.28-1.06). Confounding from variables other than age was small. Class 2 was excluded from the regression models because there were no deaths recorded from heart disease in this drinking group. The hazard ratios for classes 3 and 4 depended on only 3 and 4 heart disease deaths and might be biased because of the small number of participants and cases in these categories. Overall, risk factors other than age had little influence on the risk estimates for the alcohol categories. Although smoking status and employment status were significant and substantial risk factors for heart disease mortality in this sample, the confounding effect on the alcohol categories was very small. Marital status had a strong relation to heart disease mortality; however, it had little influence on the alcohol categories, both in bivariate and multivariate models. When an indicator for being a former drinker at baseline was included, the hazard ratios for all drinking groups were closer to one, which indicates smaller cardioprotective associations compared with lifetime abstainers. The risk for those participants who never consumed 5 or more drinks showed the strongest decrease in risk (from HR = 0.84 to 0.60). The HR for former drinking was 1.52 (95% CI 0.76-3.05). Because the frequency of heavy drinking days had a high proportion of missing values (about 20% across and within classes) for teenage years, we tested the class derivation and heart disease mortality risk using only 3 time points (20’s to 40’s). Similar classes were retrieved and conclusions about risk relationships were the same. Results were also similar when the sample was reduced to those ≥ 60 years of age and/or ischemic heart disease cases (ICD9: 410-414, ICD10: I20-I25) were used as the outcome event. When heart disease deaths occurring within 2 years of the baseline interview were excluded, the hazard ratio (HR) for
those who reported never having had 5 or more drinks compared with lifetime abstainers was similar to the full analysis sample, and the HR for those in class 1 (low heavy drinking days throughout) was closer to 1 (i.e. a reduced cardioprotective association). When heart disease deaths occurring beyond 75 years of age were excluded, the HR for never having had 5 or more drinks was almost identical to the HR using the whole analysis sample, and the HR for class 1 was much stronger in its cardioprotective association compared with lifetime abstainers (HR = 0.32 (95% CI 0.12-0.80).

Table 4-3. Heart Disease Mortality by Heavy Drinking Frequency Trajectories in Men (n = 971)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Deaths, no.</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Lifetime abstainer</td>
<td>20</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Never 5 or more drinks per day</td>
<td>14</td>
<td>1.11 (0.56-2.19)</td>
</tr>
<tr>
<td>Class 1 (steady low)</td>
<td>22</td>
<td>0.34 (0.19-0.62)</td>
</tr>
<tr>
<td>Class 2 (rise and fall)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Class 3 (steady increase)</td>
<td>3</td>
<td>0.50 (0.15-1.68)</td>
</tr>
<tr>
<td>Class 4 (steep increase)</td>
<td>4</td>
<td>0.78 (0.27-2.28)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63</td>
<td>1.10 (1.07-1.12)</td>
</tr>
<tr>
<td>Smoking status (no)</td>
<td>40</td>
<td>-</td>
</tr>
<tr>
<td>Smoking status (yes)</td>
<td>23</td>
<td>-</td>
</tr>
<tr>
<td>Employment full-time (no)</td>
<td>57</td>
<td>-</td>
</tr>
<tr>
<td>Employment full-time (yes)</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>College completed (no)</td>
<td>56</td>
<td>-</td>
</tr>
<tr>
<td>College completed (yes)</td>
<td>7</td>
<td>-</td>
</tr>
</tbody>
</table>

4.5 Discussion

To our knowledge this is the first analysis of change in heavy drinking frequency over the life course and its associated risk of heart disease mortality. In this national US sample, we
found that heavy drinking frequency did change substantially over the lifetime. However, there was no evidence from this analysis that frequency of heavy drinking from the teenage years to the forties increases the risk of dying from heart disease compared with lifetime abstainers or drinkers who never consumed 5 or more drinks in their lifetime (before the baseline interview). While conclusions for classes 2-4 were limited because of small sample size and hazard ratios should be treated with caution, the relationships among lifetime abstainers, those who never had 5 or more drinks per day (as determined by life course measurements and current consumption at baseline in 1995), and those who reported a relatively low frequency of heavy drinking days over the lifetime showed consistent associations with little confounding effects from other covariates used in this analysis. The inclusion of a risk estimate of former drinking, after life course heavy drinking was already taken into account, points to the importance of this dimension of alcohol consumption. It also showed that becoming a non-drinker seemed to increase the risk of heart disease death. Former drinking for those who have quit has consistently been shown to have a detrimental effect on heart disease risk compared with lifetime abstainers (39), the so-called sick-quitter effect (16, 40). This analysis confirms this effect.

4.5.1 Limitations

Although using quite detailed measurements of alcohol exposure, this analysis is subject to several limitations relating to survey design, the availability of potentially important covariates, and sample characteristics. For example, we had no information on past overall volume or non-heavy drinking volume. Although assessment of current alcohol intake in surveys seems to be reasonably valid (26, 41), it generally underestimates total per capita alcohol consumption in a population compared with sales statistics, despite a correlation
between the two over time (42, 43). This bias might be even stronger for retrospectively assessed heavy drinking days. Both moderate drinking and heavy drinking have been shown to vary over time (17). Although recall bias tends to result in lower reported alcohol consumption (44), retrospective assessment might paradoxically be more accurate than prospective measurement of heavy drinking (45). Apart from recall bias, current alcohol consumption might also influence reported past drinking behavior (46). Investigations of other waves of the National Alcohol Survey and the British Birth Cohort study have shown that even lifetime abstainers can be misclassified when only one measurement is used (47, 47, 48). Although accuracy of cause of death ascertainment is diminished at higher age at time of death, excluding deaths occurring beyond 75 years of age revealed similar effects to the main analysis. Our follow-up was restricted to 11 years and we cannot exclude the possibility that derived risk relationships would change if longer follow-up was available. Despite only small confounding effects from variables other than age, it is possible that other risk factors for heart disease that were not available for our analysis, such as medical history, dietary factors other than alcohol, or physical activity had an influence on the results presented in this report. Furthermore, we were not able to investigate potential interaction effects from any risk factor because of the small sample size. Although many confidence intervals included 1, small sample size might have precluded us from detecting significant effects in some drinking groups, rather than the effect estimates not being important. This is supported by the sensitivity and subgroup analyses. Lastly, using observational data we can only examine associations and so avoid statements on causality of effects.
4.5.2 Implications

Because of the small number of participants and heart disease deaths in classes 2, 3 and 4, statistical power was low and interpretation of the hazard ratios associated with these categories should be treated with caution. Nevertheless, even when these categories were combined with class 1 (low heavy drinking days throughout), the risk of mortality from heart disease was substantially lower compared to lifetime abstainers or participants who never consumed more than 5 drinks per day. Thus, based on the categorization used in this report, heavy drinking occasions over the life course showed substantial risk reduction in heart disease mortality compared with lifetime abstainers and, although less pronounced and not statistically significant, compared with drinkers who never consumed 5 or more drinks per day in their life. This suggests that occasional or very light drinking may not confer enough biochemical effect to substantially influence heart disease mortality. On the other hand, the group comprising the lowest amount of heavy drinking occasions showed the strongest cardioprotective association of all drinking groups compared with lifetime abstainers.

A study from New Zealand found somewhat similar groups of drinking over the lifetime (49). Among males, this study found a small group (4% of the sample) with a steep increase in volume per occasion from 18-26 years, while three other almost parallel classes with differing level of quantity per occasion with a slight decline after 21 years of age. Annual frequency of drinking days, however, showed quite different groupings compared to volume per occasion. Three groups with stronger increase with higher initial drinking frequency at age 18 were discovered. Identification of heavy drinking trajectories might be very different in other drinking cultures, and studies examining heavy drinking frequency over the lifetime
in these drinking cultures might be able to investigate trajectories with a higher frequency of heavy drinking better than was possible in this sample.

4.6 Conclusions

Indeed, the risk of the class with a relatively low frequency of heavy drinking days from teens to their fortiess showed a statistically significant and substantial cardioprotective association compared with lifetime abstainers. The risk of drinkers who never had a heavy drinking episode in their lifetime was lower than lifetime abstainers (not statistically significant), but higher than drinkers with a relatively low frequency of heavy drinking episodes throughout their lifetime. This indicates that the pure frequency of heavy drinking episodes before the age of forty might not be a determining factor in the alcohol-heart relationship. The sample size requirements to investigate several dimensions of alcohol exposure at baseline or over the life course are quite demanding in order to retrieve consistent and reliable risk estimates, depending on the distribution of drinking patterns within a given drinking culture. Sample size should be even larger when potential interaction effects with other risk factors for heart disease are the target of the investigation.
4.7 References


Chapter 5: Discussion

5.1 Summary

This thesis examined three aspects of alcohol intake which have potential to explain the resulting impact that alcohol use has on lifetime risk of heart disease, namely: heavy episodic drinking; separation of lifelong abstinence from cessation of drinking, and changes in alcohol use over time of follow-up within cohort studies.

Paper 1 (chapter 2) showed that HED were indeed variously defined in the literature and sometimes results were difficult to interpret. The analysis took great effort to identify and combine results of existing studies that allowed for the examination of heavy drinking episodes for quantitative analysis. This paper also systematically summarized the available epidemiological evidence on the relationship of heavy drinking episodes on heart disease. This original meta-analysis showed that individuals whose intake involved irregular heavy drinking episodes (less than 5 times per week) were consistently and substantially at higher risk of heart disease when contrasted against drinkers with a lower number of drinks per drinking day but more drinking days per week (RR = 1.43, 95% CI: 1.24-1.70). These findings were robust in several sensitivity analyses.

Statistical power for meta-regression models used in the first paper was low. Any study characteristic included in meta-regression models investigates effect modification from these characteristics because this analysis used aggregated data. Conclusions about any specific confounding effects or effect modification from other risk factors within primary studies
were not possible because such analyses were not conducted or reported. Nevertheless, assuming a strong effect modifier (in a meta-regression context) exists, the statistically significant risk for HED compared to non-HED drinkers would be divided into a lower risk for one group, and a greater one for the other group, given a dichotomous effect modifier, such as smoking status. Thus, at least one group with an even greater risk for heart disease than the pooled estimate presented in chapter 2 would have been identified. Furthermore, based on individual-level data, the analyses presented in chapter 3 or 4 did not give any indication of strong confounding effects other than age.

Using individual-level data from a large US cohort designed for alcohol assessment, paper 2 (chapter 3) presented an original secondary analysis of an important cohort study and also showed that heavy drinking episodes had a substantial and statistically significant association with elevated heart disease mortality risk among current drinkers of low to moderate average alcohol consumption for men and women. Thus, both papers 1 and 2 add strong epidemiological evidence to this literature that heavy drinking episodes in current drinkers is associated with increased heart disease risk compared to current drinkers without such drinking pattern; in particular when both drinking groups were within low to moderate average daily alcohol intake (2.5-28 g/day in men, and 2.5-14 g/day in women). A similar risk was found for former heavy drinking in men, a finding in concordance with a recent meta-analysis (1).
In this analysis, however, it was also shown that the history of the frequency of heavy drinking episodes over the life course from drinkers’ teen years to their forties did not have a detrimental effect when compared to a lifetime abstainer. Using a sub-sample of the same data set used in paper 2, paper 3 used an explorative and data-driven analysis that further investigated the relationship between changing patterns of alcohol intake over the life course and heart disease risk. This paper identified several classes of heavy drinking frequency from the teenage years to the forties. While the number of cases and participants in 3 of the 4 classes were too low to derive meaningful conclusions, the class with the lowest and relatively stable heavy drinking frequency throughout the ages studied showed a substantially lower risk of heart disease mortality compared with lifetime abstainers (HR = 0.54, 95% CI: 0.29-1.00). The risk for drinkers who had never had a heavy drinking episode in their lifetime was lower than lifetime abstainers (not statistically significant), but higher than drinkers with a relatively low frequency of heavy drinking episodes throughout their lifetime. This suggests that the simple frequency of heavy drinking episodes before the age of forty might not be the sole, or most important, determining factors in the alcohol-heart relationship.

Although some of the results from analyses in chapter 3 and 4 may seem contradictory, each of these analyses examined a different dimension of alcohol exposure and heavy drinking episodes. One heavy drinking measure (chapter 3) cannot be distinguished from pure frequency of drinking, and the other measure disregards pure drinking frequency (chapter 4) within the lifetime drinking measures because such measures were not available. In addition to the acknowledged small numbers of observations in classes of interest in chapter 4, all
analyses could have been affected by some degree of uncontrolled confounding, which is a perennial risk in observational studies. In all analyses, every effort was taken to examine and include potential confounders of the association between alcohol intake and heart disease risk. In these analyses, inclusion of known potential confounders actually had quite modest effects to alter the observed magnitude of associations between alcohol use measures and the outcome. However, the number of covariates available for such an investigation was not always complete (e.g., in chapter 2) and statistical power to address confounding (i.e., small sample sizes across relevant levels of potential confounders) was low in many analyses.

The quality of the many investigations into potential effect modifiers has been poor, mainly due to relatively low sample size and distributions of drinking behaviour in respective samples. The main issue here seems to be that effect modification both within the main exposure alcohol consumption and effect modification of these dimensions of alcohol exposure with several other risk factors for heart disease need to be investigated simultaneously. On the other hand, confounding effects from other risk factors seemed to be small in magnitude, which has been observed in other studies on average alcohol consumption (2), however, this may not be true in all drinking cultures. Little confounding effects further strengthen the evidence for a real effect of alcohol exposure on heart disease. Possibility of bias from unmeasured confounders over the life course still remains. But measurement bias was greatly reduced compared to other studies. Alcohol, by all means, has direct biochemical effects as well as social effects, both of which are extremely difficult to measure and, in addition to measurement problems in actual exposure measurement, leave many questions unanswered at this time. Age seemed to be the strongest determinant of
heart disease in the analyses presented in chapters 3 and 4 and is a strong potential effect modifier for the alcohol-heart relationship. Further effect modifiers seem possible but sample size restricted the investigation of such potential effect modification. Nevertheless, the inability to thoroughly investigate potential effect modification in the analyses of individual data leaves the causal nature of the presented effects pertaining to alcohol exposure unresolved. Careful examination of these potential effect modifiers is needed in order to inform drinking guidelines when it pertains heart disease as an outcome.

5.2 Conclusions

There is little doubt that there is some degree beneficial effect of alcohol consumption on heart disease risk, based on available epidemiological and short-term experimental evidence. In light of the obvious deleterious health and social effects of alcohol intake, this conclusion is also a cause for concern in public health because of the possibility for intentional or unintentional endorsement or encouragement to drink. This relationship has also been shown to be much more complex than limited exposure measurement (e.g., one-time assessment of current average daily intake, which is limited by reference period and assessment method) can express. Therefore, pressing questions remain about which drinking behaviour exhibits such cardioprotection and which does not. All analyses presented here supported a cardioprotective association between alcohol consumption and heart disease mortality, but each also contributed important additional information about the importance of patterns of drinking in this relationship. Paper 2 strongly supports no cardioprotective association for HED among those with average daily consumption of 2.5-28 g/day, a level generally consistent with international guidelines for what constitutes moderate or lower risk drinking (3-5), confirming all three hypotheses stated in Chapter 1. Paper 3 strongly supports a
cardioprotective association for those who reported a relatively low frequency of HED over the life course. No detrimental impact of HED frequency on heart disease in paper 3 could mean that either HED has no impact in general, or that it has no impact when occurring before the age of 40. The latter is biologically plausible in that the absolute risks of the heart disease diagnoses (related to atherosclerosis and thrombosis) most closely linked to the protective effects of ethanol are very rare under this age group, and alcohol may afford little long-term benefit relative to more acute benefits of alcohol intake on mechanisms such as clotting (6). Life course alcohol intake into a drinker’s forties may not be the most important determinant for the development of heart disease, even though intake over these years may contribute to increased long-term risk of other alcohol-related chronic diseases such as cancer (7), as well as acute risks such as trauma, which is an important contributor to the total health burden from alcohol at younger ages (8, 9). It is also possible that the frequency of drinking days may be the underlying dimension of alcohol consumption that influences the effect of alcohol on heart disease risk before or beyond forty years of age. Testing these possible explanations was beyond the focus of this analysis, and data for frequency of drinking over the life period examined here did not allow for an analysis of this dimension. The choice of life course drinking measure should ideally be based on the biochemical effect of alcohol exposure on heart disease risk. But whether this is drinking volume, drinking frequency, or frequency of heavy drinking days remains unknown to date. Thus, more observational and experimental research, simultaneously studying different dimensions of past and current consumption, is needed.
The lower limit of frequency of drinking days for the optimal limit in terms of heart disease needs to be further investigated in future studies with larger sample sizes, detailed past and present alcohol consumption patterns, and preferably with longitudinal assessment of exposure and a detailed assessment of the outcome in terms of morbidity and mortality of several sub-categories of heart disease, which were beyond the focus and possibilities of these analyses. The analyses in chapter 4 showed that a relatively low frequency of HED into drinkers’ forties did not negate the beneficial effect on heart disease mortality; however, chapter 3 indicates that the beneficial effect was restricted to those who do not participate in HED when consuming an average of 1-2 drinks per day. Given that no information on average volume or frequency of drinking days over the life course was available for analyses in chapter 4, HED must clearly be discouraged, particularly when other health outcomes related to alcohol are taken into account.

For other alcohol-related disease outcomes, the public health message for disease and injury prevention is clear. Heavy drinking episodes should be avoided altogether based on the evidence of biochemical effects of alcohol on other disease outcomes such as cancer, hypertension, and clear effects on intentional and unintentional injuries (10, 11). Guidelines in terms of heart disease risk for the general public also seem to be relatively clear. Any alcohol consumption exceeding 1 (women) and 2 (men) drinks per drinking day should be avoided because of the beneficial effect already being apparent in this range of average alcohol exposure (12), and because of the already increasing risk for many other disease outcomes with consumption exceeding these cut points. Exceeding these limits of average alcohol consumption might not be detrimental to heart disease, but it is known to be
detrimental in several other disease outcomes, and should be discouraged. This is supported by findings from this thesis, in particular for low levels of average alcohol intake, such as 1-2 drinks per day on average. It should be stressed that not all low consumption (considered only in terms of average intake) has potential beneficial effects on heart health. For example, consuming an average amount assumed to be low-risk over just 2 days of the week actually confers no benefit at all on health.

Internationally, many countries have developed low-risk drinking guidelines, based on the epidemiologic literature around alcohol and health consequences to which the three analyses in this dissertation contribute. Many such low-risk drinking guidelines refer only to average daily or weekly consumption limits (e.g., Austria, Czech Republic, Denmark, Finland, Ireland, Japan, the Netherlands (13)). Other guidelines also include daily limits, often justified in terms of risk of trauma and dependence (e.g., Australia (5), Canada (3)).

There is ample room for the improvement of drinking guidelines to better reflect the complex association between alcohol intake patterns and diverse health consequences. For example, the inclusion of age as a potential effect modifier on for heart disease risk, as the analyses presented in chapters 3 and 4 indicate that consumption behaviour at different ages might lead to different risks of heart disease. Given that many people cite heart health benefits as a reason to drink alcohol (14), and that even low levels of 1-2 drinks per day can be described as problem drinking behaviour (15), drinking guidelines should include qualifying statements about potential heart health benefits by specific drinking behaviour, such as HED.
There is ample room for the improvement of drinking guidelines to better reflect the complex association between alcohol intake patterns and diverse health consequences. For example, the inclusion of age as a potential effect modifier on heart disease risk, as the analyses presented in chapters 3 and 4 indicate that consumption behaviour at different ages might lead to different risks of heart disease. Given that many people cite heart health benefits as a reason to drink alcohol (14), and that even low levels of 1-2 drinks per day can be described as problem drinking behaviour (15), drinking guidelines should be carefully examined if there is reason to include any statements about heart health benefits of alcohol consumption and would need to include qualifying statements about a potential effect modification by specific drinking behaviour, such as HED.

5.3 Future directions

Further refinement in terms of measurement and risk modeling are necessary to improve our understanding of the alcohol-heart relationship. Future directions are manifold and should focus on differences in distributions of drinking patterns across drinking cultures, measurement of alcohol consumption in order to more clearly separate dimensions of alcohol consumption that are important for heart disease, and, perhaps most importantly, investigations of potential effect modification. Furthermore, the most often used cut point of 5 or more drinks per day for men and 4 or more drinks for women were derived from research focused on social consequences of drinking and alcohol abuse (16) and may not reflect the most appropriate threshold for effects specific to heart disease. Longitudinal studies are needed to assess the impact of time-varying covariates, including changes of
several dimensions of alcohol intake, changes in confounders and effect modifiers, and changes in health status. The results of this thesis should be replicated in other cohorts and most importantly, other drinking cultures. Investigation of potential effect modification should become a priority in alcohol-heart epidemiology, but remain a challenging endeavour because of sample size requirements.
5.4 References


Appendices
## Appendix A - Questionnaire Items (Knupfer-Series, 1995 NAS)

<table>
<thead>
<tr>
<th>CARD</th>
<th>COLS</th>
<th>VAR</th>
<th>NAME</th>
<th>QUESTION/CONTENT</th>
</tr>
</thead>
</table>
| 02   | 46-47| Q35a| ALCOHOL BOOKLET | 35a. How often do you usually have wine (or punch containing wine)?  
(WHITE PAGE OF BOOKLET)  
(USE CODES GIVEN BELOW FOR QQ. 35a-d) |
|      |      |     |       | 01 - Three or more times a day  
02 - Two times a day  
03 - Once a day  
04 - Nearly every day  
05 - Three or four times a week  
06 - Once or twice a week  
07 - Two or three times a month  
08 - About once a month  
09 - Less than once a month but at least once a year  
10 - Less than once a year  
11 - I have never had wine  
98 - Don't Know  
97, 99 - Missing |
| 48-49|      | Q35b| ALCOHOL BOOKLET | 35b. How often do you usually have beer?  
(GREEN PAGE OF BOOKLET) |
| 50-51|      | Q35c| ALCOHOL BOOKLET | 35c. How often do you usually have drinks containing whiskey or any other liquor, including scotch, bourbon, gin, vodka, run, etc.?  
(PINK PAGE OF BOOKLET) |
| 52-53|      | Q35d| ALCOHOL BOOKLET | 35d. How often do you usually have any kind of beverage containing alcohol, whether it is wine, beer, whiskey, or any other drink?  
(YELLOW PAGE OF BOOKLET) |
<table>
<thead>
<tr>
<th>CARD</th>
<th>COLS</th>
<th>NAME</th>
<th>QUESTION/CONTENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>02</td>
<td>57</td>
<td>Q36</td>
<td>36. Think of the times you have had wine recently. When you drink wine, how often do you have as many as five or six glasses: (USE CODES GIVEN BELOW FOR QQ.)</td>
</tr>
<tr>
<td>36-38)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 - Nearly every time</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 - More than half the time</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 - Less than half the time</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 - Once in a while</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5 - Never</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8 - Don't Know</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7, 9 - Missing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-8 - Inapplicable, coded 10 or 11 for Wine (Q. 35a)</td>
</tr>
<tr>
<td>58</td>
<td>Q37</td>
<td>37. When you drink wine, how often do you have only three or four glasses:</td>
<td></td>
</tr>
<tr>
<td>59</td>
<td>Q38</td>
<td>38. When you drink wine, how often do you have only one or two glasses:</td>
<td></td>
</tr>
</tbody>
</table>

**BOX 6, BEER:**
(USING THE GREEN/BEER PAGE OF BOOKLET, CHECK THE APPROPRIATE CATEGORY BELOW AND FOLLOW THE INSTRUCTIONS.)

skip to BOX 7  
ask Q.39  

| 61   | Q39  | 39. Think of all the times you have had beer recently. When you drink beer, how often do you have as many as five or six glasses or 12-ounce cans or bottles: (USE CODES GIVEN BELOW FOR QQ.) |
| 39-41) |      |      |                  |
|       |      |      | 1 - Nearly every time  |
|       |      |      | 2 - More than half the time  |
|       |      |      | 3 - Less than half the time  |
|       |      |      | 4 - Once in a while  |
|       |      |      | 5 - Never  |
|       |      |      | 8 - Don't Know  |
|       |      |      | 7, 9 - Missing  |
62 Q40 40. When you drink beer, how often do you have only three or four glasses or 12-ounce cans or bottles:

63 Q41 41. When you drink beer, how often do you have only one or two glasses or 12-ounce cans or bottles:

CARD COLS NAME QUESTION/CONTENT
02 BOX 7, WHISKEY/LIQUOR:
(USING THE PINK/WHISKEY-LIQUOR PAGE OF BOOKLET, CHECK THE APPROPRIATE CATEGORY BELOW AND FOLLOW THE INSTRUCTION.)

skip to Q.45 1. Has whiskey or any liquor less than once a year or never: (CODES 10-11).
ask Q.42 2. Has liquor at least once a year: (CODES 1-9).

65 Q42 42. Think of all the times you have had drinks containing whiskey or liquor recently. When you drink them, how often do you have as many as five or six drinks:
(USE CODES GIVEN BELOW FOR QQ. 42-44)

1 - Nearly every time
2 - More than half the time
3 - Less than half the time
4 - Once in a while
5 - Never

8 - Don't Know
7, 9 - Missing
-8 - Inapplicable, coded 10 or 11 for liquor (Q. 35c)

66 Q43 43. When you drink drinks containing whiskey or liquor, how often do you have only three or four drinks:

67 Q44 44. When you drink drinks containing whiskey or liquor, how often do you have only one or two drinks:
46a. During the last twelve months, how often did you have 12 or more drinks of any kind of alcoholic beverage in a single day, that is, any combination of cans of beer, glasses of wine, or drinks containing liquor of any kind? Was it:

01 - Every day or nearly every day,
02 - Three to four times a week,
03 - Once or twice a week,
04 - Once to three times a month,
05 - Seven to eleven times in the past year,
06 - Three to six times in the past year,
07 - Twice in the past year,
08 - Once in the past year,
09 - Never in the past year?

98 - Don't Know
97, 99 - Missing
-8 - Inapplicable, coded 1 or 2 in chk1 or coded 3-6 in Q. 45

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46b. During the last twelve months, how often did you have at least eight, but less than 12 of any kind of alcoholic beverage in a single day, that is, any combination of cans of beer, glasses of wine, or drinks containing liquor of any kind? Was it:

-8 - Inapplicable, coded 1 or 2 in chk1 or coded 4-6 in Q. 45

46c. During the last twelve months, how often did you have five, six, or seven drinks of any kind of alcoholic beverage in a single day? Was it:

-8 - Inapplicable, coded 1 or 2 in chk1 or coded 5 or 6 in Q. 45

46d. During the last twelve months, how often did you have either three drinks or four drinks of any kind of alcoholic beverage in a single day? Was it:

-8 - Inapplicable, coded 1 or 2 in chk1 or coded 6 in Q. 45
46e. During the last twelve months, how often did you have either one drink or two drinks of any kind of alcoholic beverage in a single day? Was it:

-8 - Inapplicable, coded 1 or 2 in chk1
Appendix B - Search Strategy (OVID at University of Toronto)

1. (comment or editorial or letter).pt.
2. animal/
3. human/
4. 2 not (2 and 3)
5. 4 or 1
6. (alcohol or ethanol).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
7. (heavy drinking occasion* or heavy episodic drinking or binge drinking or alcoholic intoxication or problem drinking or hangover* or irregular or pattern* or inebriation).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
8. (coronary heart disease or coronary artery disease or ischaemic heart disease or ischemic heart disease or myocardial infarction or sudden cardiac death or angina pectoris or coronary death).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
9. (case or cohort or ratio or risk* or prospective* or follow*).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
10. 6 and 7 and 8 and 9
11. 10 not 5
12. limit 11 to yr="1980 - 2008"
Appendix C - Choice of Test for Publication Bias

Never knowing the true underlying causes of small-study effects, or publication bias, the test for this unknown parameter has been challenging. Although many tests have recently been developed in this rapidly evolving field, all tests are based on certain assumptions that cause problems when epidemiological studies are the primary source of the meta-analysis. This is because the statistical tests were mainly developed for the evaluation of randomized controlled trials, and their particular usefulness in epidemiology remains largely unknown. While Begg’s (rank-based) and Egger’s (regression-based) tests are commonly used, these tests were not appropriate given the amount and structure of the data. Based on a review of the methodological literature on publication bias, the candidate decided to use Peters’ test, the most appropriate test for meta-analyses of observational studies.

Typically, all regression-based tests use some transformation of the effect size on a measure of its precision in a linear weighted regression. Higgins and Green noted recently that Begg’s test (1) is no longer recommended because it has lower power compared to Egger’s test while having the same statistical problems (2). Egger’s test (3), mathematically equivalent to an inverse-variance weighted linear regression of the log-transformed effect size on the standard error, has a high false-positive rate (type I error), and furthermore, cannot be recommended for epidemiological studies that most often use odds ratios and relative risk form adjusted regression models as the effect measure, because the odds ratio and its standard error are correlated by definition, even when no small-study effect is present (4, 5). Schwarzer (2002) noted similar high false-positive rates when Egger’s test was applied to relative risk data (6). Additionally, Egger’s test is subject to regression dilution bias (7). The correlation between the odds ratio and its standard error is the reason why Harbord et al. (8) modified Egger’s test to avoid this mathematical problem and cause of false-positive rates above nominal level. However, they also acknowledge that their test is inappropriate for adjusted effect estimates derived from epidemiological studies.

Because multiple adjusted effect sizes were abstracted from the original cohort studies in the meta-analysis in Chapter 2, generic methods were used for this meta-analysis and to test for small study effects. However, all tests for publication bias were developed with data from randomized controlled trials where this was not an issue. Therefore, the proportion of cases among controls or persons at-risk in each exposure group is not indicative of our effect estimates for the vast majority of the original studies. Therefore, both Harbord’s and Ruecker’s tests are not suited for our problem because they require specific 2x2 table input that does not consider adjusted effect estimates. Therefore, after considering all of the above, the candidate chose Peters’ test as the best fitting test for the specific analyses, which can easily be calculated by a linear regression of the log-transformed effect size against the reciprocal of the total sample size, weighted by a function of sample size among cases and controls. The data structure obtained from the primary studies further strengthens the use of this test. Peters’ test outperformed Egger’s and Harbord’s tests, as well as Macaskill’s test (an earlier test based on sample size (13)) when the odds ratio is concerned. It retains an approximate nominal false-positive rate of 10% regardless of the size of the effect, number of primary studies, or between-study heterogeneity (9). This test also has high power when the effect size, rather than statistical significance, is the cause of the funnel plot asymmetry.
Higgins and Green note that specific recommendations are almost impossible in many situations because several factors have to be taken into account, including heterogeneity, sample size distribution, and effect size. They also recommend the use of three tests when heterogeneity is below Tau-square=0.1. Among those tests are Harbord’s modified test (8), Peters’ test (9), and Ruecker’s test (10). Harbord et al. also noted that it seems that Tau-square, rather than I-square, is the determinant of statistical properties of tests for publication bias (8). While the analysis presented in Chapter 2 found moderate heterogeneity as measured by I-square (53%), Tau-square was relatively small (0.03). The results of Peters’ test showed that bias due to sample size was likely not present. Furthermore, the intercept, representing an infinitely large study showed an adjusted pooled effect of 1.28 (95% CI: 0.98, 1.66). Although not significant, one has to consider that a parameter was estimated in this regression model that should not be estimated because it was not significant. In addition, the pooled fixed- and random-effect estimates were equal in direction and similar in size, and both were statistically significant. The different methodological approaches and transformations of these tests inevitably result in different findings as many examples have shown (8, 9, 11, 12). Therefore Higgins and Green recommend choosing one test in advance (2). Nevertheless, the assumptions and low power of currently available tests for publication bias in epidemiological studies make cautious interpretation necessary, and one can never fully exclude the possibility of publication bias. Inability to explain substantial parts of the between-study heterogeneity in meta-regression models further strengthen the need for more research in this area.

References


Appendix D - Funnel Plot

Filled funnel plot with pseudo 95% confidence limits
**Appendix E - Classification of Heart Disease**

Heart disease deaths among participants analysed from the 1984 and 1995 waves of the National Alcohol Survey.

<table>
<thead>
<tr>
<th>ICD code</th>
<th>ICD-9 Description</th>
<th>Deaths (n)</th>
<th></th>
<th>male</th>
<th>female</th>
</tr>
</thead>
<tbody>
<tr>
<td>390-398</td>
<td>Acute Rheumatic Fever (390–392)</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chronic rheumatic heart disease (393–398)</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>402</td>
<td>Hypertensive heart disease</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>404</td>
<td>Hypertensive heart and renal disease</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>410-429</td>
<td>Ischemic heart disease (410–414)</td>
<td>72</td>
<td>90</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diseases of pulmonary circulation (415–417)</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other forms of heart disease (420–429)</td>
<td>25</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICD-10</td>
<td>I00-I09 Acute rheumatic fever (I00-I02)</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chronic rheumatic heart diseases (I05-I09)</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I11</td>
<td>Hypertensive heart disease</td>
<td>5</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I13</td>
<td>Hypertensive heart and renal disease</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I20-I51</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I20</td>
<td>Angina pectoris</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I21</td>
<td>Acute myocardial infarction</td>
<td>32</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I22</td>
<td>Subsequent myocardial infarction</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I23</td>
<td>Certain current complications following acute myocardial infarction</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I24</td>
<td>Other acute ischaemic heart diseases</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I25</td>
<td>Chronic ischaemic heart disease</td>
<td>38</td>
<td>45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I26-I28</td>
<td>Pulmonary heart disease and diseases of pulmonary circulation</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I30-I52</td>
<td>Other forms of heart disease</td>
<td>27</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>205</strong></td>
<td><strong>238</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Appendix F - Life Course Heavy Drinking Frequency Items

<table>
<thead>
<tr>
<th>CARD</th>
<th>COLS</th>
<th>VAR</th>
<th>NAME</th>
<th>QUESTION/CONTENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>37-38</td>
<td>Q60a</td>
<td>60a</td>
<td>How often</td>
<td>How often (do/did) you have five or more drinks on one occasion during your teens? (USE CODES GIVEN BELOW FOR QQ. 60 a-g)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(do/did)</td>
<td></td>
</tr>
<tr>
<td>01</td>
<td></td>
<td></td>
<td>Every day or nearly every day</td>
<td></td>
</tr>
<tr>
<td>02</td>
<td></td>
<td></td>
<td>Three to four times a week</td>
<td></td>
</tr>
<tr>
<td>03</td>
<td></td>
<td></td>
<td>Once or twice a week</td>
<td></td>
</tr>
<tr>
<td>04</td>
<td></td>
<td></td>
<td>Once to three times a month</td>
<td></td>
</tr>
<tr>
<td>05</td>
<td></td>
<td></td>
<td>Seven to eleven times in the past year</td>
<td></td>
</tr>
<tr>
<td>06</td>
<td></td>
<td></td>
<td>Three to six times in the past year</td>
<td></td>
</tr>
<tr>
<td>07</td>
<td></td>
<td></td>
<td>Twice in the past year</td>
<td></td>
</tr>
<tr>
<td>08</td>
<td></td>
<td></td>
<td>Once in the past year</td>
<td></td>
</tr>
<tr>
<td>09</td>
<td></td>
<td></td>
<td>Never in the past year</td>
<td></td>
</tr>
<tr>
<td>98</td>
<td></td>
<td></td>
<td>Don't Know</td>
<td></td>
</tr>
<tr>
<td>97, 99</td>
<td></td>
<td></td>
<td>Age category not applicable or Missing</td>
<td></td>
</tr>
<tr>
<td>-8</td>
<td></td>
<td></td>
<td>Inapplicable, coded 1 in chk1 or coded 1-4 or 94 in Q. 59</td>
<td></td>
</tr>
<tr>
<td>39-40</td>
<td>Q60b</td>
<td>60b</td>
<td>How often</td>
<td>How often (do/did) you have five or more drinks on one occasion now, at age 20?</td>
</tr>
<tr>
<td>41-42</td>
<td>Q60c</td>
<td>60c</td>
<td>How often</td>
<td>How often (do/did) you have five or more drinks on one occasion during your twenties?</td>
</tr>
<tr>
<td>43-44</td>
<td>Q60d</td>
<td>60d</td>
<td>How often</td>
<td>How often (do/did) you have five or more drinks on one occasion now, at age 30?</td>
</tr>
<tr>
<td>03</td>
<td></td>
<td></td>
<td>How often (do/did) you have five or more drinks on one occasion during your thirties?</td>
<td></td>
</tr>
<tr>
<td>45-46</td>
<td>Q60e</td>
<td>60e</td>
<td>How often</td>
<td>How often (do/did) you have five or more drinks on one occasion during your thirties?</td>
</tr>
<tr>
<td>47-48</td>
<td>Q60f</td>
<td>60f</td>
<td>How often</td>
<td>How often (do/did) you have five or more drinks on one occasion now, at age 40?</td>
</tr>
<tr>
<td>49-50</td>
<td>Q60g</td>
<td>60g</td>
<td>How often</td>
<td>How often (do/did) you have five or more drinks on one occasion during you forties or later?</td>
</tr>
</tbody>
</table>
Appendix G - Linkage to National Death Index

This dissertation used mortality data from the National Death Index (NDI) in combination with survey data provided by the Alcohol Research Group (ARG). In order to identify probable deaths of survey participants, for confidentiality reasons the Temple University Institute for Survey Research (IRS), which also collected the original survey data, submitted identification data to the National Death Index to establish possible mortality of individuals and obtained NDI death certificate summary data. Data collected specifically for follow-up in the original surveys used to identify deaths in the NDI were last name, first name, middle initial, month of birth, day of birth, year of birth, sex, race, marital status, state of residence, and state of birth. The NDI is a research service supported by the US National Center for Health Statistics and uses state vital statistics office’s data to compile complete lists of death records. Matched records supplied by the NDI contain date of death, state where the death occurred, and the death certificate number. Summaries of the death certificates can then be obtained from the NDI. ARG staff determined the validity of a possible match on a case-by-case basis using all variables submitted to NDI, except for last name for privacy reasons, but knowing whether this criterion has been met. Matches were confirmed with additional data from the death certificate. Underlying International Classification of Diseases (ICD) 9 and ICD 10 codes on the death certificate were used for this analysis. A dataset containing the ID number and ICD codes was provided to ARG by Temple University IRS. Using completely de-identified datasets, the candidate merged the two waves of the NAS (containing the survey data and cause of death and date of death data from the NDI) and created all analysis variables.

Linkage rates between the NDI, a database specifically developed for scientific and health research, and requests for matches have been very good in several studies with 93-98% specificity (true proportion alive detected) and 92-100% sensitivity (true proportion of deaths detected) (1, 2). Identification of death among Hispanics might not be complete because some of those participants might have returned to their country of origin and therefore could not be identified by matching via NDI (3-5). Because of known errors in detecting deaths in Hispanics who might return to their native country, a variable for Hispanics born outside the US was entered in the regression models to test for any differences in effect estimates.

References


